Supporting Information

Catalytic Asymmetric Reactions of 4-Substituted Indoles with Nitroethene: A Direct Entry to Ergot Alkaloid Structures

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Selected additional studies in the catalytic asymmetric reactions

Optimization of the catalytic asymmetric reaction with substrate 1a

**Table S1.** Screening of chiral phosphoric acid catalysts PA1-PA8 in the reaction between substrate 1a and nitroethene 2, representative results.\[a\]

| Entry | Catalyst | time (h) | Conversion (%)\[b\] | ee (%)\[c\] |
|-------|----------|----------|----------------------|-------------|
| 1     | PA1      | 48       | 90                   | 77          |
| 2     | PA2      | 18       | >90                  | 94          |
| 3     | PA3      | 48       | 88                   | 5           |
| 4     | PA4      | 22       | >90                  | 59          |
| 5     | PA5      | 22       | >90                  | 92          |
| 6     | PA6      | 22       | >90                  | 27          |
| 7     | PA7      | 22       | >90                  | 93          |
| 8     | PA8      | 22       | >90                  | 31          |

[a] Conditions: 1a (0.05 mmol), catalyst PA1-PA8 (0.005 mmol, 10 mol%), nitroethene 2 (1 – 1.5 M solution in toluene, 0.075 mmol), CH₂Cl₂ (0.25 mL), RT, then filtration on a plug of silica gel, evaporation and NMR analysis, showing the presence of a single diastereoisomer in all cases. [b] Determined by ¹H NMR analysis of the crude. [c] Determined by chiral stationary phase HPLC.

As shown in Table S1, all BINOL and VAPOL derived phosphoric acid catalysts tested were found to be able to promote the domino reaction between substrate 1a and 2, with the (R)-TRIP catalyst PA2 giving the best result in terms of enantioselectivity. It must be noted however that also the BINOL derived catalysts PA5 and PA7, derived from BINOL and bearing a 9-anthracenyl and a triphenylsilyl group at 3,3’ position, respectively, gave very good enantioselectivity in the reaction.
Table S2. Screening of reaction conditions with the (R)-TRIP catalyst PA2, representative results.^[a]\n
\[
\text{PhO} \quad \begin{array}{c}
\text{PA2 cat.,} \\
\text{solvent (0.2 M)} \\
\text{18-60 h}
\end{array} \xrightarrow{\text{NO}_2} \\
\text{PhO} \\
\text{3a: trans: cis > 95:5}
\]

\[
\text{PA2: } R = 2,4,6-(\text{Pr})_3\text{C}_6\text{H}_2 \\
\]

| Entry | Cat. mol% | Solvent | Additive | T (°C) | t (h) | Conv. (%)[^b] | 3a:3’a[^b] | ee (%)[^c] |
|-------|-----------|---------|----------|-------|------|-------------|-----------|-----------|
| 1     | 10        | CH₂Cl₂  | -        | RT    | 18   | 80          | >9:1      | 95        |
| 2     | 10        | CH₂Cl₂  | -        | RT    | 60   | >90         | >9:1      | 95        |
| 3     | 10        | toluene | -        | RT    | 60   | 87          | >9:1      | 95        |
| 4     | 10        | THF     | -        | RT    | 48   | <10         | -         | -         |
| 5     | 10        | EtOAc   | -        | RT    | 48   | <10         | -         | -         |
| 6     | 10        | CH₃CN   | -        | RT    | 48   | 22          | >9:1      | nd        |
| 7     | 5         | CH₂Cl₂  | -        | RT    | 48   | 83          | >9:1      | 95        |
| 8     | 5         | CH₂Cl₂  | -        | 0     | 48   | 59          | >9:1      | 96        |
| 9     | 5         | CH₂Cl₂  | 4 Å MS - powder | 0 | 60 | >90 | >9:1 | 96 |
| 10    | 5         | CH₂Cl₂  | 4 Å MS - powder | 0 | 60 | >90 | 1:5 | nd |
| 11    | 5         | CH₂Cl₂  | 5 Å MS - powder | 0 | 60 | >90 | >9:1 | 84 |
| 12    | 5         | CH₂Cl₂  | 5 Å MS - powder | 0 | 60 | >90 | <1:9 | - |
| 13    | 5         | CH₂Cl₂  | 3 Å MS - spheres | 0 | 60 | >90 | <1:9 | - |
| 14    | 5         | dry CH₂Cl₂ | -   | 0   | 60   | 76         | >9:1      | 97        |
| 15    | 2.5       | dry CH₂Cl₂ | MgSO₄ | 0   | 60   | 70         | >9:1      | 97        |

[^a] Conditions: indole derivative 1a (0.05 mmol), catalyst PA2, nitroethene 2 (1 – 1.5 M solution in toluene, 0.075 mmol), solvent (0.25 mL), then filtration on a plug of silica gel, evaporation and NMR analysis, showing the presence of a single diastereoisomer of 3a in all cases. [^b] Determined by ¹H NMR spectroscopy on the crude mixture. [^c] Determined by chiral stationary phase HPLC analysis.

Different solvents were initially tested (entries 1-6), showing the necessity of employing non-coordinating solvents such as CH₂Cl₂ or toluene in the reaction. CH₂Cl₂ was selected for further optimization, since toluene did not efficiently solubilize substrate 1a, and experiments not reported in Table S2 showed that this low solubilizing power resulted in even lower conversions with other substrates 1. Lowering the catalyst loading to 5 mol% worsened the conversion, especially when the reaction was performed at 0 °C (entries 7,8). Thus, drying agents were tested, in order to increase catalyst activity. Molecular sieves of different pore sizes and shapes, commonly employed in phosphoric acid catalyzed reactions, were first employed (entries 9-13). Although these drying agents did indeed increase the observed conversion, results turned out to be irreproducible, leading in some cases even to the preferential formation of the undesired side-product 3’a. Thus, dry
CH₂Cl₂ (freshly distilled from CaH₂) without additives was used as solvent, however without giving any substantial improvement (entry 14). It was finally found that a different drying agent (MgSO₄, pre-dried under vacuum with a heat-gun prior to the reaction) allowed to reach full conversion in the desired product 3a, even at 0 °C with 5 mol% catalyst loading, providing a small improvement in the enantiomeric excess of the product 3a (entry 15). Since a further lowering of the catalyst loading gave insufficient conversion (entry 16), conditions reported in entry 15 were taken as optimal to carry out the catalytic asymmetric domino reaction.
**Control experiment with side-product 3’a**

The obtainment of the side-product 3’a in some of the reactions performed in the presence of molecular sieves allowed to perform the following control experiment (Scheme S1), which showed unequivocally that catalyst PA2 is unable to resume 3’ to 3 (see the article for a relevant discussion).

![Scheme S1](image)

**Scheme S1** Control experiment with a mixture enriched in side-product 3’a.
**Products elaboration: failure of the oxidative conversion of arylketone to ester**

We carried out several attempts to unveil an ester function from arylketone 3e. Usual protocols, useful even with complex chiral compounds bearing multiple stereogenic centres, are based on the Bayer-Villiger oxidation, with \( m \)-CPBA as oxidizing agent. However, none of the conditions tested with \( m \)-CPBA afforded the desired ester product (Scheme S2). No evidence of the cleavage of the aryl-CO bond was found. We invariably observed either unreacted starting compound 3e, or extensive decomposition resulting in intractable reaction mixtures. Since these conditions are usually compatible with \( \gamma \)-nitro aryl ketones, we attributed these failures to the presence of the electron rich benzo[\( cd \)]indole core. We set up to protect of the indole NH with an electron-withdrawing group (Boc and Ts), which however proved to be much more challenging than expected, and could not be achieved with satisfactory and reproducible results. Thus, we tested different (milder) oxidative protocols on the unprotected compound 3e, namely Dakin-type oxidations which involve aqueous \( \text{H}_2\text{O}_2 \) or UHP in basic reaction media (hydroxide bases). These latter protocols did not afford the desired ester product neither. Epimerization at the \( \alpha \)-nitro stereogenic centre was instead observed, due to the highly basic reaction medium (Scheme S2).

\[ \text{3e: trans: cis} > 95:5 \]

Scheme S2 Attempts of conversion of the arylketone 3e to an ester under oxidative conditions.

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1 Q. Dai, A. Harman, J. C.-C. Zhao, *Chem. Eur. J.* **2013**, *19*, 1666.
Different unsaturated ester surrogates as Michael acceptors in substrates 1: selected results in the reactions with nitroethene 2 using catalyst PA2

All attempts to convert the ketone moiety of product 3e into an ester failed, and the reactions with substrate 1b bearing a methyl ester as the Michael acceptor did not provide the desired product 3b. Thus, to increase the synthetic usefulness of our protocol, we decided to test other ester surrogates (or masked esters) in the reaction. On the other hand, due to poor reactivity of α,β-unsaturated esters, the recourse to moieties able to activate a double bond for a conjugate addition, and then to be converted into a carboxylate ester, is a common practice in catalytic asymmetric synthesis. To select promising candidates, we explored literature data dealing with FC conjugate addition of indoles, and nitro-Michael reactions. We reasoned that i) masked esters useful for nitro-Michael reactions would possess the right reactivity to favor the desired product 3 vs side-product 3', and that ii) masked esters useful for FC addition of indoles would guarantee compatibility between the unmasking step and the indole moiety of our products 3. However, our choice had to be restricted to compounds readily prepared from 4-formylindole. This synthetic restrain forced us to abandon some otherwise promising candidates, such as acylphosphonates and acylsilanes, and resulted in the candidates shown in Figure S1. Starting from 4-formylindole, the 1-pyrrole and the 1-methylimidazole derivatives were prepared through Wittig olefination, whereas the pyridyn-2-yl-N-oxide, the α-hydroxyketone, the Meldrum’s acid and the malonate derivatives through Knoevenagel condensations. DCC-mediated couplings of the amine/amide/alcohol with the carboxylic acid derived from ester substrate 1b upon hydrolysis gave the hexafluoro-iso-propyl ester, the pyrrolidin-2-one, the oxazolidin-2-one and the succinimide substituted acceptors. The same ester 1b was reduced and then oxidized to give the aldehyde derivative. All these compounds were tested in the reaction using PA2 (5-10 mol%) as catalyst, as reported in Table S3.

Figure S1 Selected masked unsaturated esters installed at the 4-position of indole.

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2 D. Monge, H. Jiang, Y. Alvarez-Casao, *Chem. Eur. J.* 2015, 21, 4494.
Table S3. Screening of different ester surrogates with catalyst PA2, representative results.\textsuperscript{[a]}

\[ \text{Michael acceptor} \quad \text{PA2 (5-10 mol%)} \quad \text{solvent (0.2 M)} \quad \text{18-60 h} \]

![Chemical structure diagram]

| Entry | Michael acceptor | Solvent | Additive | T (°C) | t (h) | Conv. (%)\textsuperscript{[b]} | 3:3\textsuperscript{[b]} | ee 3 (%)\textsuperscript{[c]} |
|-------|------------------|---------|----------|--------|------|-----------------|----------------|----------------|
| 1     | CO₂Me            | CH₂Cl₂  | -        | RT     | 18   | 50              | <5:95          | -              |
| 2     |                  | toluene | -        | 55     | 20   | 55              | <5:95          | -              |
| 3     |                  | CH₂Cl₂  | MgSO₄    | RT     | 20   | >90 (35)\textsuperscript{[d]} | <5:95          | -              |
| 4     |                  | CH₂Cl₂  | MS 4 Å   | RT     | 24   | >90 (62)\textsuperscript{[d]} | <5:95          | -              |
| 5     | CO₂CH(CF₃)₂      | CH₂Cl₂  | -        | RT     | 18   | 35              | <5:95          | -              |
| 6     |                  | CH₂Cl₂  | -        | RT     | 60   | nd              | <5:95          | -              |
| 7     |                  | CH₂Cl₂  | MgSO₄    | RT     | 24   | 49              | <5:95          | -              |
| 8     |                  | CH₂Cl₂  | MS 4 Å   | RT     | 24   | >95 (94)\textsuperscript{[d]} | <5:95          | -              |
| 9     |                  | toluene | MS 4 Å   | 90     | 60   | >90             | 60:40\textsuperscript{[c]} | rac/rac        |
| 10    |                  | CH₂Cl₂  | -        | RT     | 60   | 15              | 1:1            | -              |
| 11    |                  | CH₂Cl₂  | MS 4 Å   | RT     | 60   | 70              | 1:2            | -              |
| 12    |                  | CH₂Cl₂  | MgSO₄    | RT     | 72   | <20             | >90:10         | nd             |
| 13    |                  | DCE     | MgSO₄    | 50     | 20   | >90             | >90:10         | nd             |
| 14    |                  | CH₂Cl₂  | MgSO₄    | 0      | 60   | >95             | >95:5          | 55             |
| 15    |                  | CH₂Cl₂  | -        | RT     | 60   | <10             | -              | -              |
| 16    |                  | toluene | MS 4 Å   | 60     | 20   | dec.            | -              | -              |
| 17    |                  | toluene | MgSO₄    | 60     | 20   | dec.            | -              | -              |
As shown in Table S3, an electron-poor hexafluoro-iso-propyl ester (entry 5) was not sufficient to drive the reaction towards the desired product 3, giving results comparable to the methyl ester (entries 1-4). An N-acyl pyrrole did not give useful results neither (entries 6-8). With this substrate, it was found that the desired product 3 could be obtained by running the reaction at higher temperatures (entry 9). However, the product was afforded as a diastereomeric mixture and in racemic form. We speculated that thermodynamic equilibration between the open chain side-product 3’ and tricyclic 3 occurred at these temperatures. Moving to 1-methyl-2-acyl imidazole as the activating moiety for the double bond, this compound was poorly reactive (entries 10-11), possibly due to the strong interactions between the acidic catalyst and the basic imidazole, “quenching” the catalyst and preventing the first step of the reaction (the FC). Even if some reactivity could be gained using molecular sieves as drying agents, nearly equimolar mixtures of product 3 and side-product 3’ were invariably obtained. A pyridin-2-yl-N-oxide ketone was then tested, considering that this ketone moiety can render an ester under (harsh) basic hydroxide conditions.

| Entry | Michael acceptor | Solvent | Additive | T (°C) | t (h) | Conv. (%)[^b] | 3:3[^b] | ee 3 (%)[^e] |
|-------|------------------|---------|----------|--------|------|--------------|--------|-------------|
| 18    | ![Image](CO2Me)  | CH₂Cl₂  | -        | RT     | 60   | >90          | >95:5  | 12          |
| 19    | ![Image](CHO)    | CH₂Cl₂  | -        | RT     | 60   | dec.         | -      | -           |
| 20    | ![Image](N-oxide)| CH₂Cl₂  | -        | RT     | 72   | <20          | <5:95  | -           |
| 21    | ![Image](N-oxide)| CH₂Cl₂  | -        | RT     | 72   | <10          | -      | -           |
| 22    | ![Image](N-oxide)| DCE     | -        | 55     | 24   | 50           | <5:95  | -           |
| 23    | ![Image](N-oxide)| CH₂Cl₂  | -        | RT     | 60   | <10          | -      | -           |
| 24    | ![Image](N-oxide)| DCE     | -        | 55     | 60   | 60           | <10    | -           |

[^a]: Conditions: indole derivative (0.05 mmol), catalyst PA2 (5-10 mol%), nitroethene 2 (1 – 1.5 M solution in toluene, 0.075-1.0 mmol), solvent (0.25 mL), then filtration on a plug of silica gel, evaporation and NMR analysis.  
[^b]: Determined by 1H NMR spectroscopy on the crude mixture.  
[^c]: Determined by chiral stationary phase HPLC analysis.  
[^d]: Yield of isolated product after chromatography on silica gel.  
[^e]: Product 3 obtained as a diastereomeric mixture (ca 1:1).
conditions, thus avoiding the oxidative Baeyer-Villiger process. The low solubility of this substrate prevented the reaction from occurring at RT, however the corresponding product 3 could be cleanly obtained by working at 55 °C in DCE (entries 12-13). It was not possible to determine the ee of this product by the available CSP HPLC. In any case, this substrate was abandoned after some preliminary tests directed at the cleavage of the pyridinyl-ketone bond in the product (hydroxides, high temperatures), led only to decomposition, without giving any evidence of the formation of the desired carboxylic acid. Palomo’s α-hydroxy ketone showed also very good reactivity and selectivity towards the desired domino product 3 but only poor enantioselectivity (entry 14). Unfortunately, a screening of phosphoric acid catalysts PA1-PA8 failed to improve the enantioselectivity of the reaction with this substrate. Possibly, the hydroxyl proton of this ketone interferes with the H-bond interactions between catalyst and substrates in the stereodetermining nitro-Michael step. Moving to a substrate bearing a highly activated Meldrum’s acid derived Michael acceptor installed on the indole, this compound did not react with nitroethene in the presence of catalyst PA2 (entries 15-17). Apparently, the strong electron withdrawing nature of this Michael acceptor completely suppressed the FC reactivity of the indole moiety. By increasing the reaction temperature, decomposition occurred. A substrate 1 bearing a less activated dicarbonyl Michael acceptor, such as an alkylidene malonate, showed instead excellent reactivity and selectivity towards the desired tricyclic product 3, which was afforded with good results in terms of conversion, but only poor enantioselectivity (entry 18). The enantioselectivity could be dramatically improved by changing the catalyst structure (see next section), and this masked ester turned out to be the substrate of choice. An aldehyde as activating moiety in the Michael acceptor was instead not suitable, since it mainly decomposed in the presence of the acidic phosphoric acid catalyst PA2 (entry 19). Moving to amides and imides as Michael acceptors, not only these substrates proved to be poorly reactive, but they gave mainly the undesired side-product 3' when some reactivity could be gained by increasing the reaction temperature (entries 20-24).

3 P. K. Singh, V. K. Singh, *Org. Lett.* **2008**, *10*, 4121.
Optimization of the catalytic asymmetric reaction with substrate 1n

Table S4. Screening of chiral phosphoric acid catalysts PA1-PA8 in the reaction between substrate 1n and nitroethene 2, representative results.[a]

| Entry | Catalyst | Conversion (%)[b] | ee (%)[c] |
|-------|----------|------------------|-----------|
| 1     | PA1      | >90              | rac       |
| 2     | PA2      | >90              | 12        |
| 3     | PA3      | >90              | 70        |
| 4     | PA4      | >90              | nd        |
| 5     | PA5      | >90              | 23        |
| 6     | PA6      | >90              | 10        |
| 7     | PA7      | >90              | 7         |
| 8     | PA8      | >90              | 10        |

[a] Conditions: 1n (0.05 mmol), catalyst PA1-PA8 (0.005 mmol, 10 mol%), nitroethene 2 (1 – 1.5 M solution in toluene, 0.10 mmol), CH2Cl2 (0.20 mL), RT, then filtration on a plug of silica gel, evaporation. [b] Determined by TLC analysis of the crude. [c] Determined by chiral stationary phase HPLC.

As shown in Table S4, all phosphoric acid catalysts tested afforded the desired tricyclic adduct 3n. However, only the 3,3’-(4-biphenyl) substituted derivative PA3 gave this product with moderate enantioselectivity (entry 3). This catalyst was thus selected for further optimization (Table S5).
Table S5. Screening of reaction conditions in the reaction of substrate 1n with nitroethene 2 catalyzed by PA3, representative results.[a]

Having selected catalyst PA3, some experiments were carried out to improve the result in terms of enantioselectivity. As shown in Table S5, dichloro methane as solvent gave better results than toluene (entries 1, 2). The enantioselectivity could be improved to a satisfactory level at the expense of the conversion by cooling the reaction mixture to 0 °C (entry 3). As in the reactions with the other substrates 1 catalyzed by PA2, the employment of MgSO4 as a mild drying agent allowed to reach at 0 °C satisfactory results also in terms of conversion (entry 4). Since a further lowering of reaction temperature (entry 5) or of catalyst loading (entry 6) was found to be unpractical, the conditions reported in entry 4 were considered as optimal for this substrate 1n.
Experimental details and products characterization

General Methods. $^1$H, $^{13}$C NMR spectra were recorded on a Varian AS 400 or 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for $^1$H and $^{13}$C NMR. $^4$ $^{13}$C NMR spectra were acquired with $^1$H broad band decoupled mode. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionisation techniques. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The Electronic Circular Dichroism spectra were recorded on a Jasco J-810 spectropolarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC, using a UV detector operating at 254 nm. The absolute and relative configuration of compound 3a and 4a was determined as outlined in the dedicated section. We assume a similar reaction pathway for compounds 3d-m, leading to the same relative and absolute configuration. Since a different catalyst was used, the absolute configuration of 3n was not assigned, whereas its trans relative configuration was confirmed by comparison with reported $^1$H NMR spectrum after decarboxylation (see below).

Materials. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Dichloromethane for the catalytic reactions was dried by filtration on a plug of basic alumina, and distillation from CaH$_2$ prior to use. 1H-Indole-4-carbaldehyde was purchased from Apollo Scientific. 2-Methyl-1H-indole-4-carbaldehyde, $^5$ 1-methyl and 1-allyl-1H-indole-4-carbaldehydes $^6$ were prepared according to the literature. Indole substrates 1a-i,k-m were synthesised through Wittig olefination, detailed as follows: the phosphonium salts, unless commercially available, were obtained by refluxing an equimolar mixture of triphenyl phosphine and the appropriate alkyl halides for a few hours in toluene or acetonitrile, and collected by filtration; the phosphorous ylides were then obtained by adding CH$_2$Cl$_2$ and the phosphonium salts in a separating funnel containing 2 M aq. NaOH; after five minutes of vigorous shaking, the organic phase was collected, dried over MgSO$_4$, filtered and evaporated affording the ylides. The ylide used in the preparation of substrate 1c was obtained following a modified literature method. $^7$ Finally, the

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$^4$ H. E. Gottlieb, V. Kotlyar, A. Nudelman, J. Org. Chem. 1997, 62, 7512.
$^5$ J. M. Muchowski, J. Heterocyclic Chem. 2000, 37, 1293.
$^6$ M. Antoine, P. Marchand, G. Le Baut, M. Czech, S. Baasner, E. Gunther, J. Enzyme Inhib. Med. 2008, 23, 686.
$^7$ B. Vakulya, S. Varga, T. Soós, J. Org. Chem. 2008, 73, 3475; the following modifications were applied: crude di(1H-pyrrol-1-yl)methanone was used directly after evaporation (no precipitation) in the second step, and $n$-BuLi instead of PhLi was used in the second step.
Wittig olefination between the indole-4-carbaldehyde and the appropriate phosphorous ylide\textsuperscript{8} was carried out in toluene or a toluene/1,4-dioxane mixture (8:2), at reflux temperature for 18-48 h;\textsuperscript{9} substrates 1 were purified by column chromatography and obtained as pure E-isomers in the case of compounds 1a,c-i,k-m, and with a 96:4 E/Z ratio in the case of 1b. Substrate 1j was prepared by an aldol condensation with pyruvic aldehyde dimethyl acetal, modifying a reported procedure.\textsuperscript{9,10} Substrate 1n was prepared by a Knoevenagel condensation following a literature protocol.\textsuperscript{11} Nitroethene 2 was obtained and stored as a toluene solution by modifying the reported procedure,\textsuperscript{12} as outlined below. (R)-TRIP catalyst PA2 was prepared from (R)-BINOL using reported procedures.\textsuperscript{13} The 3,3’-(4-biphenyl)-substituted (R)-BINOL derived phosphoric acid catalyst PA3 was prepared according to the literature.\textsuperscript{14} Racemic samples of products 3 for HPLC analysis were obtained by using diphenylphosphoric acid as catalyst (20 mol%) in CH\textsubscript{2}Cl\textsubscript{2} as solvent, at RT for 24-48 h.

**Preparation and storage of nitroethene 2.**\textsuperscript{12} Phthalic anhydride (2.8 g, 18.8 mmol) and 2-nitroethanol (0.97 mL, 12.6 mmol) are added to a Claisen apparatus, connected to a vacuum pump through a trap, and equipped after the trap with a vacuum control (Mohr clamp) and a vacuum gauge. The system is evacuated to 110 mBar, the trap immersed in a Dewar filled with liquid nitrogen, and the Claisen flask heated to 140-150 °C (pre-heated oil bath). The solid mixture turns into a brown liquid in a few minutes. Heating at this temperature is continued until ca half of the liquid in the Claisen flask is distilled. The heating temperature is then raised to 180 °C and kept at this temperature for about 10 minutes. The oil bath is then removed, the system carefully brought back to ambient pressure, and the cold trap placed under a nitrogen atmosphere and left warming to RT. Then, the yellow liquid collected in the trap is transferred by means of a Pasteur pipette and with the aid of small toluene portions into a vial. This solution is dried on powdered CaCl\textsubscript{2}, and filtered on a short plug of cotton in another vial. The concentration of nitroethane 2 in the resulting solution is determined by \textsuperscript{1}H NMR analysis (integration of nitroethane vs toluene peaks; in the calculation it is assumed that the density of this solution is the same as toluene), if needed adjusted.

\textsuperscript{8} F. Yamada, Y. Makita, M. Somei, *Heterocycles* 2007, 72, 599.
\textsuperscript{9} Olefination reactions can be conveniently followed by TLC using 2,4-dinitrophenylhydrazine stain.
\textsuperscript{10} S.-K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* 2003, 125, 9900; modification: MeOH/H\textsubscript{2}O 3:1 was used as solvent (0.70 M), and K\textsubscript{2}CO\textsubscript{3} (1 mol%) was also added in the reaction. Reflux, reaction time: 18 h.
\textsuperscript{11} H. Chen, Y. Li, C. Sheng, Z. Lv, G. Dong, T. Wang, J. Liu, M. Zhang, L. Li, T. Zhang, D. Geng, C. Niu, K. Li, *J. Med. Chem.* 2013, 56, 685.
\textsuperscript{12} D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, R. Iyengar, *J. Org. Chem.* 1980, 45, 1185.
\textsuperscript{13} M. Klussmann, L. Ratjen, S. Hoffmann, V. Wachaure, R. Goddard, B. List, *Synlett* 2010, 2189; for the last step (phosphoric acid formation): L. He, M. Bekkaye, P. Retailleau, G. Masson, *Org. Lett.* 2012, 4, 3158.
\textsuperscript{14} The procedure reported for a 9-phenantryl catalyst was applied: W. Hu, J. Zhou, X. Xu, W. Liu, L.-z. Gong, *Org. Synth.* 2011, 88, 406.
to a 1-1.5 M concentration by adding more toluene and checked again by $^1$H NMR. The solution of known concentration can be stored in a freezer (-25 °C) for several months without apparent degradation/changes in concentration, as checked by $^1$H NMR.

**General procedure for the catalytic asymmetric reaction of indoles 1 with nitroethene 2.** To a Schlenk tube equipped with a magnetic stirring bar, MgSO$_4$ (30 mg) is added. This salt is carefully thermally activated under vacuum for 5 minutes and then allowed to cool to RT. After backfilling the Schlenk tube with nitrogen, the indole derivative 1 (0.10 mmol) is added, followed by the (R)-TRIP catalyst PA2 (3.8 mg, 0.0050 mmol, 5.0 mol%), and CH$_2$Cl$_2$ (300 μL). The mixture is cooled to 0 °C and allowed to stir for 5 minutes, then nitroethene 2 (0.15 mmol, x μL of a 1-1.5 M toluene solution) is added in one portion. The mixture is then stirred at this temperature for 60 h, then filtered through a short plug of silica gel, and the plug washed with Et$_2$O (4x). After concentration of the solvents, the residue is analysed by $^1$H NMR spectroscopy to determine the diastereomeric ratio of the adducts 3. Finally, the residue is purified by chromatography on silica gel, affording pure products 3.

1-((4R,5R)-4-Nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)-1-phenylethanone (3a)

Following the general procedure, the title compound was obtained as a white solid in 95% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t$_{maj}$ = 35.4 min, t$_{min}$ = 30.4 min, 97% ee). $^1$H NMR (CDCl$_3$, 400 MHz) δ = 8.06 (br s, 1H), 7.96-7.93 (m, 2H), 7.62-7.56 (m, 1H), 7.50-7.44 (m, 2H), 7.21 (br d, J = 8.0 Hz, 1H), 7.14 (br t, J = 8.0 Hz, 1H), 6.96-6.93 (m, 1H), 6.83 (d, J = 7.1 Hz, 1H), 5.24 (dt, J$_t$ = 5.8 Hz, J$_d$ = 4.4 Hz, 1H), 4.65 (q, J = 6.2 Hz, 1H), 3.79 (dd, J = 16.0, 5.7 Hz, 1H), 3.43 (dd, J = 18.1, 6.0 Hz, 1H), 3.40 (ddd, J = 16.2, 4.3, 1.1 Hz, 1H), 3.33 (dd, J = 18.1, 7.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ = 197.2, 136.5, 133.7, 133.5, 129.6, 128.8, 128.1, 124.8, 123.6, 118.9, 116.0, 109.5, 107.3, 85.4, 41.9, 36.9, 25.1; [α]$_D^{25}$ = -107 (c = 0.586 in CH$_2$Cl$_2$); ESIMS = 343 (M + Na$^+$).
Methyl 3-(3-(2-nitroethyl)-1H-indol-4-yl)acrylate (3’b)

Following the general procedure but performing the reaction at RT for 24 h in the presence of 4 Å MS (45 mg) instead of MgSO₄, the title compound was obtained as a pale yellow solid in 62% yield, after chromatography on silica gel (CH₂Cl₂). ¹H NMR analysis of the crude mixture showed a 96:4 E/Z ratio, corresponding to the E/Z ratio of the starting substrate 1b. ¹H NMR (CDCl₃, 400 MHz) δ = [signals of the E-isomer] 8.36 (d, J = 16.1 Hz, 1H), 8.29 (br s, 1H), 7.44-7.37 (m, 2H), 7.27-7.18 (m, 1H), 7.13 (br s, 1H), 6.48 (d, J = 15.7 Hz, 1H), 4.70 (t, J = 6.8 Hz, 2H), 3.84 (s, 3H), 3.65 (t, J = 6.5 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ = [signals of the E-isomer] 167.4, 142.6, 137.2, 127.6, 124.9, 124.7, 122.6, 119.3, 118.8, 113.4, 110.3, 75.8, 51.8, 25.7; ESIMS = 297 (M + Na⁺).

(E)-3-(3-(2-Nitroethyl)-1H-indol-4-yl)-1-(1H-pyrrol-1-yl)prop-2-en-1-one (3’e)

Following the general procedure but performing the reaction at RT for 20 h in the presence of 4 Å MS (45 mg) instead of MgSO₄, the title compound was obtained as a yellow solid in 94% yield, after chromatography on silica gel (CH₂Cl₂). ¹H NMR analysis of the crude mixture showed a single E stereoisomer. ¹H NMR (acetone-d₆, 400 MHz) δ = 10.55 (br s, 1H), 8.77 (d, J = 15.2 Hz, 1H), 7.78-7.72 (m, 3H), 7.62-7.58 (m, 2H), 7.43 (br s, 1H), 7.25 (t, J = 8.1 Hz, 1H), 6.42-6.40 (m, 2H), 4.97 (t, J = 7.5 Hz, 2H), 3.77 (t, J = 7.45 Hz, 2H); ¹³C NMR (acetone-d₆, 100 MHz) δ = 163.6, 146.2, 138.7, 128.2, 126.8, 126.4, 122.6, 120.9, 119.7, 117.5, 115.3, 115.2, 113.7, 110.8, 76.4, 26.4; ESIMS = 332 (M + Na⁺).

1-((4R,5R)-4-Nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)propan-2-one (3d)

Following the general procedure, the title compound was obtained as a pale yellow solid in 96% yield, after chromatography on silica gel (CH₂Cl₂). ¹H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, tₘₐₓ = 30.1 min, tₘᵢⁿ = 24.6 min, 54% ee). ¹H NMR (CDCl₃, 400 MHz) δ = 8.05 (br s, 1H), 7.21-7.11 (m, 2H), 6.93 (br s, 1H), 6.83 (br d, J = 7.1 Hz, 1H), 5.07 (dt, J₁ = 6.2 Hz, J₂ = 4.8 Hz, 1H), 4.39 (br q, J = 5.9 Hz, 1H), 3.71 (dd, J = 16.1, 6.3 Hz, 1H), 3.35 (dd, J = 17.0, 4.5 Hz, 1H), 2.90 (dd, J = 17.6, 6.0 Hz, 1H), 2.80 (dd, J = 18.2, 6.0 Hz, 1H), 2.19 (s, 3H); ¹³C NMR (CDCl₃, 100
MHz) $\delta = 205.7, 133.6, 129.2, 124.7, 123.5, 118.8, 115.7, 109.5, 107.2, 85.5, 46.2, 36.8, 30.4, 25.3$; $[\alpha]_D^{25} = -47$ (c = 0.436 in CH$_2$Cl$_2$); ESIMS = 281 (M + Na$^+$).

1-(4-Methoxyphenyl)-2-((4$R,5R$)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)ethanone (3e)

Following the general procedure, the title compound was obtained as a white solid in 91% yield, after chromatography on silica gel (CH$_2$Cl$_2$ + 1% Et$_2$O). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, $\lambda$ 254 nm, $t_{\text{maj}} = 63.9$ min, $t_{\text{min}} = 53.1$ min, 97% ee). $^1$H NMR (CDCl$_3$, 600 MHz) $\delta = 8.12$ (br s, 1H), 7.95-7.90 (m, 2H), 7.19-7.10 (m, 2H), 6.94-6.90 (m, 3H), 6.88 (d, J = 7.2 Hz, 1H), 5.23 (br q, $J = 5.6$ Hz, 1H), 4.63 (br q, $J = 6.2$ Hz, 1H), 3.86 (s, 1H), 3.77 (dd, $J = 17.8$, 6.8 Hz, 1H), 3.47-3.36 (m, 2H), 3.24 (dd, $J = 17.8$, 6.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta = 195.7, 163.8, 133.6, 130.4, 129.6, 129.5, 124.7, 123.4, 118.9, 115.9, 113.8, 109.5, 107.2, 85.4, 55.5, 41.6, 37.0, 24.9$; $[\alpha]_D^{25} = -140$ (c = 0.472 in CH$_2$Cl$_2$); ESIMS = 373 (M + Na$^+$).

1-(4-Bromophenyl)-2-((4$R,5R$)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)ethanone (3f)

Following the general procedure, the title compound was obtained as a white solid in 95% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, $\lambda$ 254 nm, $t_{\text{maj}} = 39.4$ min, $t_{\text{min}} = 35.8$ min, 97% ee). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta = 8.01$ (br s, 1H), 7.74-7.70 (m, 2H), 7.54-7.49 (m, 2H), 7.15-7.02 (m, 2H), 6.89 (br s, 1H), 6.79-6.74 (m, 1H), 5.13 (dt, $J_t = 5.7$ Hz, $J_d = 4.4$ Hz, 1H), 4.53 (q, $J = 6.1$ Hz, 1H), 3.70 (dd, $J = 16.8$, 6.3 Hz, 1H), 3.39-3.29 (m, 2H), 3.20 (dd, $J = 18.2$, 6.3 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta = 196.1, 135.2, 133.7, 132.0, 129.6, 129.3, 128.8, 124.7, 123.5, 119.0, 115.9, 109.6, 107.2, 85.4, 41.6, 36.9, 25.2$; $[\alpha]_D^{25} = -85$ (c = 0.580 in CH$_2$Cl$_2$); ESIMS = 421-423 (M + Na$^+$).
2-((4R,5R)-4-Nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)-1-(p-tolyl)ethanone (3g)

Following the general procedure, the title compound was obtained as a white solid in 98% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, $n$-hexane/i-PrOH 80:20, flow 0.75 mL/min, $\lambda$ 254 nm, $t_{maj} = 35.8$ min, $t_{min} = 30.5$ min, 98% ee). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 8.06 (br s, 1H), 7.88-7.81 (m, 2H), 7.29-7.08 (m, 4H), 6.94 (br s, 1H), 6.90-6.84 (m, 1H), 5.22 (q, $J$ = 5.6 Hz, 1H), 4.62 (q, $J$ = 6.2 Hz, 1H), 3.77 (dd, $J$ = 16.7, 5.8 Hz, 1H), 3.53-3.35 (m, 2H), 3.27 (dd, $J$ = 18.0, 7.2 Hz, 1H), 2.40 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 196.8, 144.5, 134.1, 133.7, 130.0, 129.4, 128.2, 124.8, 123.5, 119.0, 116.0, 109.5, 107.3, 85.4, 41.8, 37.0, 25.1, 21.7; $\left[\alpha\right]_D^{25}$ = -186 (c = 0.560 in CH$_2$Cl$_2$); ESIMS = 357 (M + Na$^+$).

1-(Naphthalen-2-yl)-2-((4R,5R)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)ethanone (3h)

Following the general procedure, the title compound was obtained as a white solid in 98% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, $n$-hexane/i-PrOH 80:20, flow 0.75 mL/min, $\lambda$ 254 nm, $t_{maj} = 46.2$ min, $t_{min} = 27.0$ min, 99% ee). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 8.44 (br s, 1H), 8.12-8.01 (m, 2H), 7.95-7.85 (m, 3H), 7.65-7.51 (m, 2H), 7.23-7.11 (m, 2H), 7.02-6.90 (m, 2H), 5.27 (br q, $J$ = 5.3 Hz, 1H), 4.70 (q, $J$ = 5.9 Hz, 1H), 3.79 (dd, $J$ = 16.8, 6.0 Hz, 1H), 3.61 (dd, $J$ = 17.9, 5.7 Hz, 1H), 3.50-3.40 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ = 197.1, 135.8, 133.8, 133.7, 132.4, 130.0, 129.6, 128.8, 128.7, 127.8, 127.0, 124.8, 123.7, 123.6, 119.0, 116.1, 110.0, 107.3, 85.4, 42.0, 37.0, 25.1; $\left[\alpha\right]_D^{25}$ = -110 (c = 0.793 in CH$_2$Cl$_2$); ESIMS = 393 (M + Na$^+$).

3,3-Dimethyl-1-((4R,5R)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)butan-2-one (3i)

Following the general procedure, the title compound was obtained as a white solid in 90% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary
phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 13.5 min, t_{min} = 11.3 min, 93% ee). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ = 8.03 (br s, 1H), 7.23-7.12 (m, 2H), 6.97 (br s, 1H), 6.81 (br d, J = 6.9 Hz, 1H), 5.10 (q, J = 6.9 Hz, 1H), 4.43 (q, J = 6.2 Hz, 1H), 3.77 (dd, J = 16.6, 5.9 Hz, 1H), 3.32 (br dd, J = 16.4, 4.5 Hz, 1H), 2.96 (dd, J = 18.2, 5.9 Hz, 1H), 2.83 (dd, J = 18.3, 7.0 Hz, 1H), 1.13 (s, 9H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ = 213.0, 133.7, 129.7, 124.7, 123.5, 118.8, 116.0, 109.4, 107.3, 85.2, 44.3, 40.1, 36.6, 26.4, 24.9; [α]D\textsuperscript{25} = -93 (c = 0.500 in CH\textsubscript{2}Cl\textsubscript{2}); ESIMS = 323 (M + Na\textsuperscript{+}).

\textbf{1,1-Dimethoxy-3-((4R,5R)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)propan-2-one (3j)}

Following the general procedure, but performing the reaction at RT for 24 h, the title compound was obtained as a white solid in 82% yield, after chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}). \textsuperscript{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 27.5 min, t_{min} = 18.8 min, 96% ee). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ = 8.03 (br s, 1H), 7.25-7.10 (m, 2H), 6.96 (br s, 1H), 6.86 (br d, J = 7.0 Hz, 1H), 5.09 (dt, J\textsubscript{t} = 6.1 Hz, J\textsubscript{d} = 4.5 Hz, 1H), 4.43 (s, 1H), 4.42 (q, J = 6.1 Hz, 1H), 3.73 (br dd, J = 16.1, 5.9 Hz, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.44-3.35 (m, 1H), 3.05 (dd, J = 19.3, 6.5 Hz, 1H), 3.00 (dd, J = 19.7, 6.3 Hz, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ = 203.0, 133.7, 129.2, 124.7, 123.5, 118.8, 115.9, 109.5, 107.4, 104.5, 85.4, 55.2, 55.1, 40.0, 36.1, 25.3; [α]D\textsuperscript{25} = -36 (c = 0.39 in CH\textsubscript{2}Cl\textsubscript{2}); ESIMS = 341 (M + Na\textsuperscript{+}).

\textbf{2-((4R,5R)-2-Methyl-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)-1-phenylethanone (3k)}

Following the general procedure, the title compound was obtained as a white solid in 90% yield, after chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}). \textsuperscript{1}H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, t_{maj} = 33.4 min, t_{min} = 26.1 min, 94% ee). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ = 8.00-7.92 (m, 2H), 7.80 (br s, 1H), 7.62-7.56 (m, 1H), 7.50-7.43 (m, 2H), 7.12-7.01 (m, 2H), 6.83 (br d, J = 6.3 Hz, 1H), 5.19 (br q, J = 6.0 Hz, 1H), 4.58 (br q, J = 5.9 Hz, 1H), 3.65 (dd, J = 16.2, 6.2 Hz 1H), 3.45 (dd, J = 17.9, 5.8 Hz, 1H), 3.35-3.22 (m, 2H), 2.35 (s, 3H); \textsuperscript{13}C NMR
(CDCl$_3$, 100 MHz) $\delta = 197.3$, 136.6, 133.5, 133.3, 129.2, 128.7, 128.5, 128.1, 125.8, 122.4, 115.8, 108.7, 103.4, 85.5, 41.8, 36.9, 24.7, 11.6; $[\alpha]^\text{D}_{25} = -184$ (c = 0.524 in CH$_2$Cl$_2$); ESIMS = 357 (M + Na$^+$).

2-((4$R$,5$R$)-1-Methyl-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)-1-phenylethanone (3l)

Following the general procedure but using 2.25 equiv. of nitroethene 2, the title compound was obtained as a white solid in 75% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, $\lambda$ 254 nm, $t_{\text{maj}} = 46.8$ min, $t_{\text{min}} = 35.9$ min, 95% ee). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta = 7.97$-7.92 (m, 2H), 7.61-7.54 (m, 1H), 7.49-7.42 (m, 2H), 7.19-7.12 (m, 2H), 6.88-6.80 (m, 2H), 5.22 (br q, $J = 5.6$ Hz, 1H), 4.63 (br q, $J = 6.1$ Hz, 1H), 3.78 (dd, $J = 16.5$, 5.8 Hz, 1H), 3.75 (s, 3H), 3.47 (dd, $J = 18.1$, 5.8 Hz, 1H), 3.40 (dd, $J = 16.2$, 4.1 Hz, 1H), 3.30 (dd, $J = 18.1$, 7.0 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta = 197.1$, 136.5, 134.8, 133.5, 129.7, 128.7, 128.1, 125.1, 123.6, 123.1, 115.4, 107.8, 105.9, 85.4, 41.9, 36.9, 32.9, 25.0; $[\alpha]^\text{D}_{25} = -102$ (c = 0.332 in CH$_2$Cl$_2$); ESIMS = 357 (M + Na$^+$).

2-((4$R$,5$R$)-1-Allyl-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)-1-phenylethanone (3m)

Following the general procedure but using 7.5 mol% ($R$)-TRIP catalyst, 2 equiv. of nitroethene 2 and at RT, the title compound was obtained as a white solid in 70% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak AS column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, $\lambda$ 254 nm, $t_{\text{maj}} = 31.8$ min, $t_{\text{min}} = 26.1$ min, 93% ee). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta = 7.96$ (bd, $J = 8.1$ Hz, 2H), 7.58 (bt, $J = 7.0$ Hz, 1H), 7.46 (bt, $J = 7.3$ Hz, 2H), 7.15-7.12 (m, 2H), 6.89-6.84 (m, 2H), 6.03-5.95 (m, 1H), 5.28-5.10 (m, 3H), 4.72-4.65 (m, 2H), 4.63 (bq, $J = 6.1$ Hz, 1H), 3.78 (dd, $J = 16.1$, 6.1 Hz, 1H), 3.48 (dd, $J = 17.9$, 5.8 Hz, 1H), 3.41 (dd, $J = 15.8$, 4.2 Hz, 1H), 3.32 (dd, $J = 17.6$, 7.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta = 197.1$, 136.5, 134.2, 133.5, 133.5, 129.8, 128.7, 128.0, 125.3, 123.1, 122.5, 117.5, 115.5, 108.2, 106.3, 85.4, 49.1, 41.9, 36.9, 25.1; $[\alpha]^\text{D}_{25} = -75$ (c = 0.334 in CH$_2$Cl$_2$); ESIMS = 360 (M + Na$^+$).
Dimethyl 2-((4R*,5R*)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)malonate (3n)

Following the general procedure but using 10 mol% 3,3’-(4-biphenyl) (R)-BINOL derived phosphoric acid catalyst PA3 and 2 equiv. of nitroethene 2, the title compound was obtained as a pale yellow foam in 86% yield, after chromatography on silica gel (CH$_2$Cl$_2$). $^1$H NMR analysis of the crude mixture showed the presence of a single diastereoisomer. The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak ADH column, n-hexane/i-PrOH 90:10, flow 0.75 mL/min, $\lambda$ 254 nm, $t_{maj} =$ 41.2 min, $t_{min} =$ 44.1 min, 83% ee). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta =$ 8.06 (br s, 1H), 7.20 (br d, J = 8.3 Hz, 1H), 7.11 (br t, J = 8.0 Hz, 1H), 6.96 (br s, 1H), 6.91 (br d, J = 7.0 Hz, 1H), 5.22 (br q, J = 3.4 Hz, 1H), 4.80 (dd, J = 10.9, 3.4 Hz, 1H), 3.90 (dd, J = 17.8, 3.0 Hz, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 3.57 (d, J = 10.5 Hz, 1H), 3.34 (br dd, J = 17.5, 4.3 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta =$ 167.8, 167.5, 133.9, 125.4, 124.5, 123.2, 119.3, 117.8, 110.4, 106.5, 83.1, 55.8, 53.1, 52.7, 40.2, 23.6; [$\alpha$]$_D^{25}$ = +87 (c = 0.520 in CH$_2$Cl$_2$); ESI-MS = 355 (M + Na$^+$).
Preparation of compound 4a (1-((4S,5R)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)-1-phenylethanone) via base promoted epimerisation. In a vial equipped with a magnetic stirring bar, compound 3a (0.072 mmol, 97% ee) was dissolved in MeOH (200 μL), and the resulting solution cooled to 0 °C with stirring. A NaOH solution in MeOH (268 μL of a solution prepared dissolving 96 mg NaOH in 1.5 mL of MeOH, 0.43 mmol, 6 equiv.) was added, the reaction allowed to warm to RT. After 2 h stirring, it was judged by TLC (n-hexane/Et₂O 3/7) that the diastereomeric mixture had reached the equilibrium composition. The mixture was diluted with Et₂O, sat. aq. NH₄Cl was added, the phases separated, and the aqueous phase extracted with EtOAc (3 x). The combined organic extracts were dried by filtration on a Celite® plug, evaporated and analysed by ¹H NMR spectroscopy, which showed a 91:9 diastereomeric ratio favouring the cis-isomer 4a. The product was purified by chromatography on silica gel (n-hexane/EtOAc 35:65), affording an analytically pure sample of the title compound as a white solid accompanied by its diastereomeric mixture with the starting 3a (overall 92% yield). The enantiomeric excess of the product was determined by chiral stationary phase HPLC (Chiralpak ADH column, n-hexane/i-PrOH 80:20, flow 0.75 mL/min, λ 254 nm, tₘaj = 23.2 min, tₘin = 20.4 min, 96% ee), showing that epimerisation occurred without racemisation, under these conditions. Optical rotation was not measured due to the very small amount of diastereomerically pure compound available. ¹H NMR (acetone-d₆, 600 MHz) δ = 10.07 (br s, 1H), 8.01 (br d, J = 8.3 Hz, 1H), 7.60 (br t, J = 8.3 Hz, 1H), 7.49 (br t, J = 8.4 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 7.16 (br s, 1H), 7.02 (br t, J = 8.3 Hz, 1H), 6.86 (br d, J = 8.3 Hz, 1H), 5.32 (br quint, J = 4.0 Hz, 1H), 4.60 (br quint, J = 4.0 Hz, 1H), 3.67 (ddd, J = 15.9, 9.2, 1.7 Hz, 1H), 3.62 (br dd, J = 15.5, 7.4 Hz, 1H), 3.59 (dd, J = 15.9, 4.9 Hz, 1H), 3.36 (br dd, J = 17.6, 3.9 Hz, 1H); ¹³C NMR (acetone-d₆, 150 MHz) δ = 198.7, 138.7, 135.6, 134.6, 131.9, 130.2, 129.6, 126.9, 124.0, 121.1, 117.0, 111.2, 108.9, 87.0, 41.0, 38.5, 31.1, 26.1; ESIMS = 343 (M + Na⁺).
Preparation of compound 3b (methyl 2-((4R*,5R*)-4-nitro-1,3,4,5-tetrahydrobenzo[cd]indol-5-yl)acetate) via hydrolysis, decarboxylation and esterification of 3n\textsuperscript{15} In a vial equipped with a magnetic stirring bar, compound 3n (0.090 mmol) was suspended in MeOH (600 μL), and cooled to ca -10 °C (ice-acetone bath). An aq. 1 M LiOH solution (300 μL, 0.30 mmol, 3.3 equiv.) was added, and the resulting mixture stirred at the same temperature for 4 h, then at RT for additional 4 h. EtOAc was then added, followed by H₂O and 0.5 M aq. KHSO₄ until pH < 1. The organic phase was separated, and the aqueous phase extracted with EtOAc (3x). The combined organic phases were dried by filtration on a short plug of Celite® and evaporated to dryness under reduced pressure in a 50 mL round bottom flask. The thus obtained di-acid was suspended in toluene (2 mL), a magnetic stirring bar was added to the flask, a cooler was applied and the system heated to 110 °C using a pre-heated oil bath for 2 h. The mixture was then cooled to RT, and evaporated to dryness under reduced pressure. The residue was suspended in MeOH (1 mL) and toluene (1 mL), and a 2 M solution of TMSCHN₂ in Et₂O (120 μL, 0.24 mmol, CAUTION! Highly toxic and explosive) was added while stirring. The reaction mixture was left stirring at RT for 30 min, then evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica gel (CH₂Cl₂), affording the title compound as a pale yellow solid in 48% yield over the three steps, and as a 87:13 diastereomeric mixture favouring the trans-isomer 3b over the cis-isomer. The enantiomeric excess of the trans-product 3b was determined by chiral stationary phase HPLC (Chiralpak ADH column, n-hexane/i-PrOH 90:10, flow 0.75 mL/min, λ 254 nm, tₘaj = 30.4 min, tₘin = 33.0 min, 82% ee), showing that racemization did not occur under these conditions. \textsuperscript{1}H NMR (CDCl₃, 400 MHz) δ [signals of the trans-isomer] = 8.02 (br s, 1H), 7.23 (br d, J = 8.2 Hz, 1H), 7.17 (br t, J = 7.4 Hz, 1H), 6.98 (br s, 1H), 6.94 (br d, J = 7.1 Hz, 1H), 5.18 (dt, Jₜ = 6.4 Hz, J₅ = 4.4 Hz, 1H), 4.35 (q, J = 6.7 Hz, 1H), 3.75 (dd, J = 15.7, 6.1 Hz, 1H), 3.72 (s, 3H), 3.43 (ddd, J = 16.0, 4.3, 0.9 Hz, 1H), 2.80 (dd, J = 16.6, 6.2 Hz, 1H), 2.76 (dd, J = 16.6, 6.5 Hz, 1H); \textsuperscript{13}C NMR (CDCl₃, 100 MHz) δ [signals of the trans-isomer] = 171.5, 133.7, 128.6, 123.6, 118.8, 115.8, 109.7, 107.3, 85.4, 52.0, 37.9, 37.1, 25.4; ESIMS = 297 (M + Na\textsuperscript{+}). \textsuperscript{1}H NMR spectroscopic data for this compound are in accordance with literature,\textsuperscript{8} thus substantiating the assignment of the relative configuration of the major diastereoisomer 3b (and of the parent compound 3n) as 4,5-trans.

\textsuperscript{15} Procedure adapted from: O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, Chem. Eur. J. 2007, 13, 8338. It turned out to be better to use MeOH instead of THF during the hydrolytic step.
Conformational analysis and determination of the relative and absolute configuration of compounds 3a and 4a

All the attempts to obtain good crystals of the prepared compounds 3 were not successful. For this reason the relative and absolute configuration was determined by a combination of conformational analysis and theoretical simulations of chirooptical spectra. Compound 3a was selected as representative compound.

![Chemical structure of 3a](image)

**Relative configuration**

The relative stereochemistry of the two stereogenic centres at C-4 and C-5 of compound 3a and of its diastereoisomer 4a was determined by means of NMR spectroscopy. Full assignment of the $^1$H and $^{13}$C spectra was preliminarily achieved by bi-dimensional experiments (COSY, gHSQC and gHMBC), taken in CDCl$_3$ solutions for 3a and acetone-$d_6$ for 4a.

**Compound 3a.**

The two diastereotopic hydrogens belonging to C-3 were found at 3.45 ($^2$J$_{HH}$ = 16.9 Hz, $^3$J$_{HH}$ = 4.2 Hz) and 3.73 ppm ($^2$J$_{HH}$ = 16.9, $^3$J$_{HH}$ = 4.2 Hz) whereas the two diastereotopic hydrogens belonging to C-9 at 3.41 ppm ($^2$J$_{HH}$ = 18.2 Hz, $^3$J$_{HH}$ = 6.9 Hz) were assigned by long-range correlation with the carbonyl signal. The CH signal at 4.59 ppm was assigned to the H-5 hydrogen by long range correlation with the carbonyl signal, and the signal at 5.29 ppm was therefore assigned to H-4. The pattern of the latter is a quartet generated by three very similar $^3$J$_{HH}$ coupling constants (about 5.0 Hz) with H-5 and with H-3’ and H-3’’. This feature suggests that H-5 should occupies a pseudo-equatorial position, where anti-periplanar dihedral angle with other hydrogens are not available. The signal of the NH (7.98 ppm) was assigned by the lack of correlation in the $^1$H-$^{13}$C HSQC spectrum. DPFGSE-NOE experiments$^{16}$ were acquired in order to assign the relative stereochemistry at C-4 and C-5 (Figure S2).

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$^{16}$ K. Stott, J. Stonehouse, J. Keeler, T-L. Hwang, A. J. Shaka, *J. Am. Chem. Soc.* **1995**, *117*, 4199.
Figure S2: DPFGSE-NOE spectra of 3a (600 MHz in CDCl₃, +25°C). Bottom: ¹H-NMR control spectrum. Traces a-d: red labels indicate the saturation point. Green labels indicate “control” NOEs, that have to be observed to assure reliable results. Blue labels indicate diagnostic NOEs.

On saturation of the H-4 signal (trace a), NOE enhancements with similar intensity were observed for H-5, H-3’,H-3” and both the H-9 signals. On saturation of the H-5 signal (trace b), large NOEs were observed on H-4 and H-9 and only a small enhancement was observed for one of the H-3 hydrogens at 3.73 ppm (H-3’). The observed NOEs suggested that H-5 occupies a pseudo-equatorial position, otherwise a strong NOE should be observed on one of the H-3 signals, due to 1-3 diaxial relationship (the observation of the small NOE on H-3’ is due to the presence of a second
conformation with smaller population, see below). As a confirmation, the saturation of the signal of H-3” (in a pseudo-axial position) at 3.41 ppm yields a noticeable NOE enhancement on the H-9 hydrogens (trace d), that occupies a pseudo-axial position on the ring, too. All the NOE data thus agree to assign the 4R*,5R* relative configuration (i.e. a trans relationship).

**Compound 4a**

In the case of 4a the signal of H-4 was found at 5.21 ppm, while that of H-5 was at 4.50 ppm (both CH signals were assigned by HSQC). The pattern of both signals was a doublet of triplets, with $^3J_{HH} = 8.6$ and 4.3 Hz for H-4 and 8.5 and 4.3 Hz for H-5. The large coupling constant of H-4 corresponds to a $^3J$ with one of the H-3 hydrogens and that of H-5 is with one of the H-9 hydrogens. The H-4/H-5 $^3J$ coupling constant is 4.3 Hz. This small value implies that H-4 occupies a pseudo-axial position, where it can develop a large coupling constant with one of the H-3 hydrogen, the dihedral angle between them being close to 180°. On the other hand, the small $^3J$ between H-4 and H-5 suggests that the latter is in the equatorial position, with a H-C-C-H dihedral with H-4 close to 60°, thus a cis relationship of the substituents.

As a cross check, NOE spectra were acquired also for compound 4a (Figure S3). On saturation of the H-4 signal a noticeable NOE effect was observed on one of the H-9 hydrogens (H-9’, trace a). When H-5 was saturated the NOE was observed on H-3”, i.e. the hydrogen that occupies the pseudo-axial position. This NOE is observable only when also H-5 is in a pseudo-axial position. On the other hand, when H-9’ was saturated a NOE enhancement was observed for H-3’. Also this NOE can be effective only when the H-9 hydrogens are in a pseudo-axial position (and therefore H-5 in a pseudo-equatorial position). This mismatch clearly indicates that the observed NOEs are the result of averaging between two different conformations of the cycle (see below).
Figure S3: DPFGSE-NOE spectra of 4a (600 MHz in acetone-$d_6$). Bottom: $^1$H-NMR control spectrum. Red labels indicate the saturation point. Green label indicate “control” NOEs, that have to be observed to assure reliable results. Blue labels indicate diagnostic NOEs. The dotted line marks the chemical shift of the H-9” hydrogen.

Variable Temperature NMR spectra of 4a

The NMR spectrum of 4a recorded at +25 °C showed some broad signals (H-9”), probably due to the ring inversion that is not fast in the NMR timescale. To get information about the conformational rearrangement, a CD$_2$Cl$_2$ sample of 4a was cooled to -80 °C. On lowering the
At temperatures below -50 °C, the aliphatic signals (and some aromatic signals as well) broaden, coalesce, and split into two sets of signals. At -80 °C, the ratio of the signals is 64:36 (Figure S4). In particular, the signal of H-4 was split into two signals at 5.12 ppm (major) and 5.50 ppm (minor), and the signal of H-5 was split into signals at 4.74 ppm (major) and 4.36 ppm (minor).

Figure S4. $^1$H spectra (600 MHz in CD$_2$Cl$_2$) of the aliphatic region of 4a. Top trace: spectrum recorded at +25 °C. Bottom: spectrum recorded at -80 °C showing the presence of two conformers with 64:36 ratio. Asterisks in the spectra indicate the $^{13}$C satellites of the residual signal of the deuterated solvent.

The pattern of the major signal of H-4 is a doublet of triplets with a very large coupling constant (12.0 Hz) with one of the H-3 hydrogens, indicating the trans-diaxial relationship of the two hydrogens. On the contrary, only small coupling constants are observed for the same signal of the
minor conformer, confirming that in the minor conformation the H-4 is in a pseudo-equatorial position. The small H-4/H-5 coupling constant (≈ 4 Hz) confirmed the gauche relationship between the two hydrogens, thus a cis relationship (4R*, 5S* relative configuration). The energy barrier involved in the conformational exchange was evaluated at the coalescence temperature of the H-5 signal (-33 °C) as 11.0 ± 0.2 kcal/mol. The 64:36 ratio at -80 °C corresponds to a ΔG°= 0.22 kcal/mol. Considering ΔG° invariant with the temperature and applying Boltzmann distribution, the conformational ratio to be considered at ambient temperature is 59:41.

Variable Temperature NMR spectra of 3a

The same VT-NMR approach was employed for compound 3a. The ring inversion barrier was found to be lower with respect to 4a and the conformers ratio was more unbalanced. On lowering the temperature below -50 °C a broadening of the lines of H-4 and H-5 was observed, reaching the maximum linewidth at -110 °C, eventually followed by a sharpening of the same lines. This is the classical behaviour of a conformational exchange within two widely unbalanced conformations. At -140 °C a second set of signals was detected, accounting for a 97:3 ratio of the two conformations (Figure S5).

The line broadening of the signals due to the very low temperature did not allow for a direct measure of the coupling constants of H-4 and H-5, but the line of the H-4 signal (≈ 13 Hz at -140 °C) is too narrow to hide large coupling constants (if a line broadening is applied to the -50 °C spectrum the same signal has a linewidth of 14 Hz). This implies that in the more populated conformation the H-4 hydrogen occupies a pseudo-equatorial position, where only small coupling constants can be effective with the neighboring hydrogens. The 97:3 ratio at -140 °C corresponded to a ΔG° = 0.86 kcal/mol. If ΔG° is kept constant with the temperature the conformational ratio at ambient temperature is 81:19. The presence of a second populated conformation where H-5 is in the axial position well explains the weak NOE observed for H-3’ (trace b of Figure S2).

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17 J. Sandstrom, Dynamic NMR Spectroscopy. Academic Press, 1982, p. 81. See also L. Lunazzi, A. Mazzanti, D. Casarini, O. De Lucchi, F. Fabris, J. Org. Chem. 2000, 65, 883.
Figure S5. $^1$H spectra (CDFCl$_2$, 600 MHz) of the aliphatic region of 3a. Top trace: spectrum recorded at -50 °C. Bottom: spectrum recorded at -140 °C showing the presence of two conformations with 97:3 ratio (see the inset spectrum on the left). Asterisk in the spectra indicates an impurity of the deuterated solvent.
Conformational analysis of 3a and 4a

Although the rigidity of the heterocyclic core of compound 3a and 4a and the VT-NMR data provided very good information, the conformational degrees of freedom due to the CH$_2$COPh moiety still represents an issue for the conformational analysis step needed to tackle the absolute configuration determination.

As the first stage, we performed a conformational search on compound 3a (trans), with the 4$R^*,5R^*$ relative configuration. The whole conformational space was explored by means of Monte Carlo searching together with the MMFF94 molecular mechanics force field as implemented in Titan 1.0.5 (Wavefunction inc.).

![Structure of 3a](image)

All the conformations found by MM search within a 10 kcal/mol window were then optimized using DFT at the M06-2X/6-31++G(d,p) level and at the M06-2X/6-31+G(d,p) by including the solvent (acetonitrile) with the PCM model using the Gaussian 09 suite of programs. The harmonic vibrational frequencies of each optimized conformation were calculated at the same level to confirm their stability (no imaginary frequencies were observed) and to evaluate the relative energy of each conformation. After DFT minimization, four conformations were found to be enclosed in a 2 kcal/mol window, as reported in Table S6. All of them exhibit the same shape of the six-membered ring, that corresponds to a pseudo boat conformation with the carbon bearing the NO$_2$ group out of the plane. Two conformations have the CH in a pseudo-axial conformation while the second pair has the CH in the pseudo-equatorial position (i.e. NO$_2$ in the axial position). Within each pair the conformations are different because of the disposition of the CH$_2$COPh moiety (Figure S6). The relative electronic energies and enthalpies suggested that all these conformations should be

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populated.\textsuperscript{21} Whereas the gas-phase calculations gave unreliable results, probably due to the large difference of the large dipole moment of the molecule in the different conformations, the PCM optimization showed a clear preference for one of the equatorial conformations, matching well the experimental observations.

Table S6. Relative energies of the four conformations of 3a evaluated using ZPE-corrected enthalpies and PCM-M06-2X/6-31+G(d,p) using acetonitrile as solvent. Theoretical populations were calculated using Boltzmann distribution at 298 °K. Experimental ratios of the two pairs were determined by VT-NMR.

| Conformation | $\Delta H^\circ$ | Calcd. | Exptl. |
|--------------|-----------------|--------|--------|
|              | PCM-M06-2X/6-31+G(d,p) | Populations | Populations |
| Eq-1         | 0.00            | 68     | 81     |
| Eq-2         | 2.29            | 1      |        |
| Ax-1         | 0.96            | 13     | 19     |
| Ax-2         | 0.78            | 18     |        |

Figure S6. 3D view of the four conformations of compound 3a.

In the case of compound 4a (\textit{cis}) the MM conformational search found three conformations they were subsequently optimized at the PCM-M06-2X/6-31+G(d,p) level using acetonitrile as the

\textsuperscript{21} It has been pointed out that the calculations of entropy data are often thwarted by the existence of low-frequency vibrational modes, thus the calculation of the free Gibbs Energy is not reliable. See: a) Y. Lan, K. N. Houk, \textit{J. Am. Chem. Soc.} \textbf{2010}, \textit{132}, 17921. b) C. P. A. Anconi, C. S. Nascimento Jr, H. F. Dos Santos, W. B. De Almeida, \textit{Chem. Phys. Lett.} \textbf{2006}, \textit{418}, 459. c) J. P. Guthrie, \textit{J. Phys. Chem. A} \textbf{2001}, \textit{105}, 8495. d) M. W. Wong, \textit{Chem. Phys. Lett.} \textbf{1996}, \textit{256}, 391; e) S. E. Wheeler, A. J. McNeil, P. Muller, T. M. Swager, K. N. Houk, \textit{J. Am. Chem. Soc} \textbf{2010}, \textit{132}, 3304.
solvent (Table S7 and Figure S7).

**Table S7.** Relative energies of the three conformations of 4a evaluated using ZPE-corrected enthalpies and PCM-M06-2X/6-31+G(d,p) using acetonitrile as solvent. Theoretical populations were calculated using Boltzmann distribution at 298 °K. Experimental ratio of the two pair were determined by VT-NMR.

| Conformation | $\Delta H^\circ$ | Calcd. Population | Exptl. Population |
|--------------|------------------|-------------------|-------------------|
| Eq-1         | 0.00             | 41                | 45                |
| Eq-2         | 0.43             | 19                |                   |
| Ax-1         | 0.02             | 39                | 55                |

**Figure S7.** 3D view of the three conformations of compound 4a.

Also in this case the calculations including the solvent (acetonitrile) well agree with the experimental populations. Within the pair in which the H-4 is equatorial the conformations are different because of the different dispositions of the nitro group with respect to the group in position 5. On the contrary, in the axial conformation the nitro group has only one preferred conformation.
Absolute configuration

Having in hand the relative configuration and suitable experimental data supporting the preferred conformations, the assignment of the absolute configuration was pursued by chirooptical methods.

The determination of the absolute configuration (AC) of chiral molecules using chirooptical techniques like optical rotation (OR), electronic circular dichroism (ECD), and vibrational circular dichroism (VCD) has gained feasibility and reliability because of the development of methods for the prediction of these properties based on density functional theory (DFT) and on its Time-Dependent formalism (TD-DFT). In the present case the theoretical calculation of the electronic circular dichroism spectra (ECD) was selected for the absolute configuration assignment.

The electronic excitation energies and rotational strengths have been calculated for the isolated molecule in the gas phase for the four conformations of \( 3a \) using TD-DFT with four different methods (functionals), to ascertain whether different computational approaches provide different shapes of the simulated spectra (see Figure S8). Simulations were performed with the hybrid functionals BH&HLYP and M06-2X, with oB97XD that includes empirical dispersion, and CAM-B3LYP that includes long range correction using the Coulomb Attenuating Method. The calculations employed the 6-311++G(2d,p) basis set that proved many times to be sufficiently accurate at a reasonable computational cost. Rotational strengths were calculated in both length and velocity representation, the resulting values being very similar (RMS differences < 5%). For this reason the errors due to basis set incompleteness should be very small. Although the spectra simulated within the same functional for the four conformations are quite different, they are nevertheless consistent with the simulation of a negative Cotton effect at about 190 nm (Figure S8).

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Figure S8. TD-DFT simulated spectra calculated for the four conformations of 3a using four different functionals (CAM-B3LYP, BH&HLYP, M06-2X, oB97-XD) and the same 6-311++G(2d,p) basis set. For each conformation the first 60 excited states were calculated, and the spectrum was obtained using a 0.33 eV line width at half height.

The population-weighted spectra to be compared with the experimental spectrum were obtained using the experimental ratio measured by VT-NMR. This accounts for the experimental ratio between the two conformations due to ring inversion, but NMR data do not provide information about the conformational ratio due to the different dispositions of the CH2COPh moiety within each conformational pair. For this reason these ratios were calculated using the relative enthalpies within each pair, keeping constant the overall Eq:Ax ratio as 80:20. The final ratio employed for the to generate the conformationally averaged spectrum was 70:10:13:7 (Eq-1:Eq-2:Ax-1:Ax-2). As shown in Figure S9, the simulated spectra match very well the Cotton effects at 270, 230 and 200 nm when the 4R,5R absolute configuration was assumed in the calculations.
Figure S9 Simulations of the experimental ECD spectrum of 3a. For each quarter, the black line correspond to the experimental spectrum (acetonitrile solution, 1.1·10^{-4} M, 0.2 cm path length, Δε in Mol L^{-1} cm^{-1}) and the colored line to the TD-DFT simulation (6-311++G(2d,p) basis set). The simulated spectra were vertically scaled and red-shifted by 7-14 nm to get the best match with the experimental spectrum. All the simulations are for the 4R,5R absolute configuration.

The same theoretical approach were applied to compound 4a (Figures S10 and S11). In this case the conformational ratio employed in the simulation of the experimental ECD spectrum was that derived from VT-NMR for the Eq:Ax ratio and that suggested by calculations for the Eq-1:Eq-2 ratio. The final population ratio employed was 32:15:53 (Eq-1:Eq-2:Ax-1). Again the simulated spectrum fitted very well the experimental one when the 4S,5R absolute configuration is considered. This result confirms that epimerization occurred at C-4.
Figure S10. TD-DFT simulated spectra calculated for the four conformations of 4a using four different functionals (CAM-B3LYP, BH&HLYP, M06-2X, ωB97-XD) and the same 6-311++G(2d,p) basis set. For each conformation the first 60 excited states were calculated, and the spectrum was obtained using a 0.33 eV line width at half height.

Figure S11 Simulations of the experimental ECD spectrum of 4a. For each quarter, the black line correspond to the experimental spectrum (acetonitrile solution, 1.2·10⁻⁴M, 0.2 cm path length Δε in Mol L⁻¹ cm⁻¹) and the colored line to the TD-DFT simulation (6-311++G(2d,p) basis set). The simulated spectra were vertically scaled and red-shifted by 7-14 nm to get the best match with the experimental spectrum. All the simulations are for the 4S,5R absolute configuration.
Additional material: COSY of 4a at -80 °C:
Computational studies on the reaction pathway

Computational methods

All calculations reported in the present mechanistic study were carried out using density functional theory with the B3LYP functional, as implemented in the Gaussian09 program package. Geometry optimizations were performed using the 6-31G(d,p) basis set for all atoms. Single-point energy calculations were then performed for each of these optimized structures with the 6-311+G(2d,2p) basis set. The stationary points were confirmed as minima (no imaginary frequencies) or transition states (only one imaginary frequency) by analytical frequency calculations at the same theory level as the geometry optimizations. All calculations, including geometry optimizations and frequency calculations, were performed in solvent phase using the conductor-like polarizable continuum model (CPCM) method with the UFF radii and with the parameters for dichloromethane. The reported energies are Gibbs free energies, which include zero-point vibrational corrections, thermal and entropy corrections at 298 K, solvation energies and dispersion effects. The latter are calculated using the B3LYP-D3 method of Grimme, with BJ damping.

Pathway for the formation of product cis-4

For comparison, we optimized the transition states leading to the formation of the cis stereoisomer of the product, not observed under standard reaction conditions (Figure S12).

Starting from INT2 the cyclization affording the cis product could occur through TS3_cis. This is 3.6 kcal/mol higher in energy compared to the corresponding transition state (TS3) leading to the formation of the trans diastereoisomer. According to these results the reaction should afford exclusively trans product 3, in agreement with the experiments.

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**Reaction of ester-substituted indole 1b**

Experimentally, the reaction on ester-substituted indole 1b afforded exclusively the open-chain adduct 3'b. To test whether the suggested mechanism can also account for this fact, we optimized the transition states for the cyclization (TS3_ester, analogous to TS3) and for the nitronic acid-nitrotautomerization giving the open-chain product (TS3'ester, analogous to TS3'). The tautomerization has essentially the same energy barrier as when occurring on the ketone-substituted indole (Figure S13). As expected, the nature of the substituent does not affect this barrier, while it influences substantially the barrier for the cyclization. In fact, the cyclization occurring on the ester-substituted intermediate is ca. 8 kcal/mol higher in energy compared to the same step occurring on the ketone-substituted intermediate (TS3_ester vs. TS3). This is consistent with the notion that the ester is a weaker Michael acceptor than the ketone. However, the calculations still predict the formation of the cyclized product to be favored, in contrast to the experimental outcome. This inconsistency is probably due to the computed tautomerization TS3', and can have different possible explanations. One possibility is that the computational approach used here leads to an overestimation of the energy of TS3'ester. Another possibility is that the tautomerization leading to the open-chain adduct 3'b occurs through a different mechanism, with the possible involvement of other species present in solution. Several other mechanistic possibilities were tested, including a tautomerization mediated by two or three water molecules, the involvement of one water molecule in the phosphoric acid catalyzed tautomerization, and possible stepwise processes. We found these possibilities to be associated with higher energy barriers. Moreover, due to the inclusion of more species (i.e. water molecules) or the separation of charged species, these results are likely to be associated with higher computational errors.
Since TS3' and TS3'_{ester} are very similar, it is likely that our calculations give an overestimation of the energy computed for TS3' also for the ketone derived substrate. Considering the experimental outcome of the reactions and the calculated barriers for TS3 and TS3_{ester}, a more realistic value for the energy barriers of the tautomerization step lies between 13 and 18 kcal/mol. Nevertheless, we feel that the overall computational results give a reliable qualitative picture over the actual reaction pathway.

**Figure S13:** Selected points in the free energy profile for the reaction occurring on the ester-substituted indole 1b.
Optimized structures and Cartesian coordinates of stationary points

- (E)-4-(1H-indol-4-yl)but-3-en-2-one (1d)

B3LYP/6-311+G(2d,2p) energy:
-594.06171002 a.u.
ZPE: 0.200715 a.u.
Thermal correction to Gibbs Free Energy: 0.160812 a.u.
Dispersion correction: -30.86 kcal/mol

C     2.61315700    0.12750800   -0.00043900
C     1.29452000   -0.41827100    0.00013300
C     0.17799500    0.46323400    0.00160900
C     0.44262600    1.84260700    0.00271000
C     1.74996600    2.34956900    0.00214300
C     2.85756100    1.50217600    0.00050000
C     2.78903900   -2.11224600   -0.00235300
C     1.44128100   -1.84591900   -0.00152600
H    -0.38483500    2.54459200    0.00463800
H     1.90131700    3.42461700    0.00324600
H     3.86924100    1.89625900    0.00024200
H     4.50188100   -0.85450400   -0.00197800
H     3.30787100   -3.06007300   -0.00342200
N     3.49647000   -0.93076600   -0.00173500
C    -1.17282200   -0.08910700    0.00214200
H    -1.22159600   -1.17536300   -0.00173500
C     0.59134500   -0.64616400   -0.00066800
H     0.63904100   -1.72266600   -0.00162500
N      0.55362600    0.02825000   -0.00036200
O    -0.78540200    1.12972500    0.92448900
O     0.87687200   -0.16149000   -0.98984400
C    -1.50562200    0.04078100    0.41170000
C    -0.82191800   -1.11201800   -0.00821230
C    -2.89473700    0.11778100    0.43253400
C    -1.60624800   -2.20504800   -0.41728300
C    -3.64594300   -0.98331200    0.02287400
P     0.07100900    2.07302500   -0.06762700
O    -0.64125500    3.06559800   -0.89812000
O      1.0193100    2.64804400    1.01513200
O      1.37892500    3.55197900    0.80102500
O     0.78540200    1.12972500    0.92448900
O     0.87687200   -0.16149000   -0.98984400
C    -1.50562200    0.04078100    0.41170000
C    -0.82191800   -1.11201800   -0.00821230
C    -2.89473700    0.11778100    0.43253400
C    -1.60624800   -2.20504800   -0.41728300
C    -3.64594300   -0.98331200    0.02287400
P     0.07100900    2.07302500   -0.06762700
O    -0.64125500    3.06559800   -0.89812000
O      1.0193100    2.64804400    1.01513200
O      1.37892500    3.55197900    0.80102500
C    -1.50562200    0.04078100    0.41170000
C    -0.82191800   -1.11201800   -0.00821230
C    -2.89473700    0.11778100    0.43253400
C    -1.60624800   -2.20504800   -0.41728300
C    -3.64594300   -0.98331200    0.02287400
H     0.71949800   -3.18575500    0.80576400
H     0.71949800   -3.18575500    0.80576400

- Catalyst

B3LYP/6-311+G(2d,2p) energy:
-1105.32940491 a.u.
ZPE: 0.189888 a.u.
Thermal correction to Gibbs Free Energy: 0.150128 a.u.
Dispersion correction: -39.72 kcal/mol

- 2
B3LYP/6-311+G(2d,2p) energy:
-1,982.5830246800 a.u.
ZPE: 0.448131 a.u.
Thermal correction to Gibbs Free Energy: 0.380628 a.u.
Dispersion correction: -89.67 kcal/mol

- TS1

B3LYP/6-311+G(2d,2p) energy:
-1,982.6019542000 a.u.
ZPE: 0.450213 a.u.
Thermal correction to Gibbs Free Energy: 0.383843 a.u.
Dispersion correction: -89.79 kcal/mol
C    -3.17051000   -3.98414300    1.03264100  
C    -3.32671500   -1.18516900    0.67488000  
O    -1.14641600    0.38395800   -0.29337500  
H     0.11065300    1.12756800   -3.25712800  
O    -1.19141300    0.28582600   -2.89986600  
O     0.23722600   -1.36449500   -1.44701470  
P    -1.02984400   -0.52989000   -1.64632800  

Dispersion correction: -94.86 kcal/mol  
Thermal correction to Gibbs Free Energy: 0.3824 a.u.  
ZPE: 0.446663 a.u.  

- TS2  

B3LYP/6-311+G(2d,2p) energy:  
-1.982.5714623300 a.u.  
ZPE: 0.446663 a.u.  
Thermal correction to Gibbs Free Energy: 0.3824 a.u.  
Dispersion correction: -94.86 kcal/mol  

- INT2  

B3LYP/6-311+G(2d,2p) energy:  
-1.982.6173128200 a.u.  
ZPE: 0.450213 a.u.  

S43
Thermal correction to Gibbs Free Energy: 0.383325 a.u.
Dispersion correction: -89.03 kcal/mol

| H     | -0.05595200 | -1.87069800 | -0.78933800 |
| C     | 7.01313400  | -0.51256900 | 0.37674500  |
| C     | 5.64087900  | -0.31386000 | 0.03457600  |
| C     | 5.16162600  | 1.02269100  | -0.09115900 |
| H     | 6.07179200  | 2.06622500  | 0.13920000  |
| C     | 7.41244900  | 1.83344500  | 0.47919800  |
| C     | 7.90535900  | 0.53816800  | 0.60247300  |
| C     | 6.08294600  | -2.53194400 | 0.09779100  |
| H     | 5.07043200  | -1.63054700 | -0.14523800 |
| H     | 5.71764700  | 3.90948900  | 0.08622100  |
| H     | 8.07018000  | 2.67816700  | 0.65876900  |
| H     | 8.94100500  | 0.34826800  | 0.86717300  |
| H     | 8.12861100  | -2.30902200 | 0.61241700  |
| H     | 6.05655700  | -3.61159500 | 0.09475400  |
| N     | -0.52492700 | -0.93877700 | 1.40712600  |
| N     | 7.24259400  | -1.87000000 | 0.41595600  |
| C     | 3.78586900  | 1.30943300  | -0.42883400 |
| C     | 3.04657500  | 0.53589200  | 0.17752500  |
| C     | 3.30374900  | 2.43914400  | -1.00946300 |
| H     | 3.98347800  | 3.22985400  | 1.31970000  |
| C     | 1.88698500  | 2.72307200  | -1.30275200 |
| C     | 0.81506200  | 1.72021700  | -0.91370300 |
| H     | 1.01277600  | 0.72834300  | -1.33245100 |
| H     | 0.76552800  | 1.60750800  | 0.17486800  |
| H     | -0.14994400 | 2.07540300  | 1.27720800  |
| O     | 1.58296600  | 3.78017000  | -1.85573400 |
| O     | 3.67136300  | -2.03013300 | -0.53361200 |
| H     | 3.68656000  | -3.06192300 | -0.91192400 |
| H     | 3.29647000  | -1.42339900 | 1.36492600  |
| C     | 2.70188500  | -1.96291800 | 0.61223500  |
| H     | 3.02266800  | -1.95977700 | 1.64529400  |
| N     | 1.41461300  | -1.95888500 | 0.45368500  |
| O     | 0.54419100  | 1.97816900  | 1.40660900  |
| O     | 0.94873500  | -1.98363200 | -0.84073900 |
| P     | -2.27149300 | -0.70583700 | 0.15050900  |
| O     | -1.36342700 | -0.33131200 | 1.37098500  |
| O     | -1.62004400 | -1.54136200 | -0.90604600 |
| O     | -2.82880500 | 0.66127400  | -0.49745300 |
| O     | -3.57828200 | -1.35669000 | 0.84371300  |
| C     | -3.75268400 | 1.48786000  | 0.17143300  |
| C     | -5.08067700 | 1.05212900  | 0.33697300  |
| C     | -3.32327100 | 2.74297200  | 0.56326600  |
| C     | -5.97510700 | 1.96316300  | 0.39216700  |
| C     | -4.23434200 | 3.62622900  | 1.14126500  |
| C     | -2.28808700 | 0.30192400  | 0.40051700  |
| C     | -5.56299500 | 3.23378600  | 1.32122000  |
| C     | -7.00369200 | 1.65546700  | 1.08470400  |
| C     | -3.90539500 | 4.16366300  | 1.44893500  |
| C     | -6.27648400 | 3.91336600  | 1.77633700  |
| C     | -4.78706700 | -1.44720100 | 0.12604400  |
| C     | -5.21613900 | -2.71185400 | -0.25702500 |
| C     | -5.54093400 | -2.88313300 | -0.10006500 |
| C     | -6.45129900 | -2.84499100 | -0.89074200 |
| C     | -4.59037500 | -3.57185100 | -0.04470000 |
| C     | -6.78057600 | -0.45395200 | -0.74325900 |
| C     | -7.23319400 | -1.71275600 | -1.13274000 |
| H     | -6.79789700 | -3.82789900 | -1.19350800 |
| H     | -7.38337500 | 0.42459100  | -0.95025700 |

H     | -8.19228800 | -1.80859500 | -1.63224800 |

Thermal correction to Gibbs Free Energy: 0.386586 a.u.
Dispersion correction: -96.21 kcal/mol
| Atom  | X          | Y          | Z          |
|-------|------------|------------|------------|
| O     | 1.50790100 | -2.21674700 | 0.80954100 |
| O     | 1.55811800 | 0.28452100  | -2.28452100 |
| O     | 3.12215900 | -1.10158200 | 0.80954100 |
| C     | 1.94498300 | 1.46331900  | -0.13582700 |
| C     | 3.08319900 | 1.72533300  | -0.35514900 |
| C     | 0.95186900 | 2.38594200  | -0.45284700 |
| C     | 3.63793400 | 2.96942100  | -1.01112600 |
| H     | -0.08303300 | 2.13767800  | -0.24305000 |
| C     | 2.65574100 | 3.90297900  | -1.24616000 |
| C     | 4.68137600 | 3.19276000  | -1.12096000 |
| C     | 0.53932200 | 4.33590400  | -1.26065100 |
| H     | 2.94094400 | 4.85303000  | -1.68487000 |
| C     | 4.23582800 | -0.62292400 | -0.23539500 |
| C     | 5.23337900 | 1.18229600  | 0.09608500  |
| C     | 4.36442500 | 0.75350000  | 0.01777600  |
| H     | 5.55636300 | 1.18229600  | 0.09608500  |
| C     | 6.40532900 | -1.08009900 | 0.69935300  |
| H     | 5.08349500 | -2.58446200 | -0.13343100 |
| C     | 4.65757500 | -0.28282800 | -0.52939500 |
| C     | 7.18649800 | -1.78051000 | 0.96015300  |
| H     | 5.67735000 | 2.23724000  | 0.85346600  |
| C     | 4.72701000 | 0.64345700  | 1.43871400  |

- INT3

B3LYP/6-311+G(2d,2p) energy:
-1,982.62062515 a.u.
ZPE: 0.45501 a.u.
Thermal correction to Gibbs Free Energy: 0.39076 a.u.
Dispersion correction: -92.81 kcal/mol

H    0.18715900  -1.49678300  -1.84348600
C    -4.22335900  2.51657500   0.77501400
C    -3.84333300  1.24995500  -0.28213000
C    -3.22060600  0.28287100  -1.07912000
C    -2.98301300  0.61693500  -2.40846300
C    -3.37698500  1.88051100  -2.91110300
C    -3.99508300  2.84800500  -2.11815400
C    -4.73128400  2.38731700  -1.24936600
C    -4.16942600  1.17651100  -1.10347000
H    -2.49519600  -0.09405200  3.06840300
H    -3.18375500  2.10708500  -3.95582000
H    -4.27853700  3.81206300  -2.52921600
H    -5.13896400  4.13185200  -0.27682700
H    -5.11323900  2.75693600  -2.37043800
H    0.33077500  -0.03942800  1.42783800
N    -4.77193600  3.19301400  -0.29718500

- TS4

B3LYP/6-311+G(2d,2p) energy:
--1,982.59905156 a.u.
ZPE: 0.449926 a.u.
Thermal correction to Gibbs Free Energy: 0.38640 a.u.
| Element | X        | Y        | Z        |
|---------|----------|----------|----------|
| H       | 0.34596600 | -0.65650100 | 0.87539200 |
| C       | 5.99374800 | 0.08470300 | -1.35561200 |
| C       | 4.88204800 | 0.26259300 | -0.50401900 |
| C       | 3.93815300 | -0.74286300 | -0.26390900 |
| C       | 4.13989100 | -1.95644400 | -0.91549200 |
| C       | 5.26526260 | -2.14556800 | -1.75800600 |
| C       | 6.20205030 | -1.14418500 | -1.99693600 |
| C       | 5.99516000 | 2.20431300 | -0.55607600 |
| C       | 4.89311100 | 1.59629900 | -0.00614300 |
| H       | 3.43737700 | -2.77555900 | -0.79701800 |
| H       | 5.38853400 | -3.10877600 | -2.24386700 |
| H       | 7.04855200 | -1.31436000 | -2.65547300 |
| H       | 7.50136100 | 1.49679200 | -1.88706200 |
| H       | 6.37294000 | 3.21090300 | -0.48347900 |
| H       | -0.23167000 | -2.84215800 | -0.05864000 |
| N       | 6.66484500 | 1.29105300 | -1.36303000 |
| C       | 2.79905100 | -0.39608700 | 0.70138120 |
| C       | 3.13941100 | -0.60838500 | 1.72241200 |
| C       | 1.50320020 | -1.20429000 | 0.41754400 |
| C       | 1.22333600 | -1.17256800 | -0.63257200 |
| C       | 1.34246100 | -2.46339600 | 1.01436800 |
| H       | 1.71316300 | -3.91879500 | 2.52965600 |
| H       | 3.16194200 | -3.01671600 | 2.00412400 |
| O       | 0.39738100 | -3.27559800 | 0.62011800 |
| C       | 3.80038900 | 2.02154400 | 0.92589200 |
| H       | 3.52494700 | 3.07342300 | 0.84314700 |
| C       | 4.09091400 | 1.88703000 | 1.97522500 |
| C       | 2.54789700 | 1.13948100 | 0.65054900 |
| H       | 2.09753400 | 4.26182800 | -0.30153400 |
| N       | 1.52706700 | 1.55657300 | 1.68996700 |
| O       | 0.77773800 | 2.48391000 | 1.39578600 |
| C       | 0.54813400 | 0.99449460 | 2.78410600 |
| P       | -1.79723600 | -0.78952600 | -0.00629800 |
| O       | -0.82150700 | -0.24472600 | 1.05020300 |
| O       | -1.33590400 | -0.99303000 | -0.77886700 |
| O       | -2.18812800 | 0.35210400 | -1.09515600 |
| O       | -3.18713000 | -0.99528700 | 0.81109100 |
| C       | -2.92171400 | 1.47897900 | -0.71059900 |
| C       | -4.29571800 | 1.35630700 | -0.44216700 |
| C       | -2.26987900 | 2.70899800 | -0.69360300 |
| C       | -5.00381100 | 2.53920000 | -0.16689300 |
| C       | -2.99815400 | 3.86559600 | -0.46140000 |
| H       | -1.20529800 | 2.74394400 | -0.89746500 |
| C       | -4.36835500 | 3.77929900 | -0.15612500 |
| H       | -6.06325000 | 2.47338300 | 0.06113800 |
| C       | -2.94544300 | 4.82749800 | -0.40084900 |
| H       | -4.93978800 | 4.67521000 | 0.06491800 |
| C       | -4.40350500 | -1.09987500 | 0.12790300 |
| C       | -5.04917000 | -2.33292500 | 0.13765900 |
| C       | -4.97909000 | 0.04908800 | -0.45862000 |
| C       | -6.30963700 | -2.45223280 | -0.44839300 |
| C       | -4.56336000 | -3.17715900 | 0.61428500 |
| C       | -6.24888100 | -1.10024000 | -1.04281300 |
| C       | -6.90928400 | -1.33175300 | -1.03915300 |
| H       | -6.81728400 | -3.41173000 | -0.44331000 |
| H       | -6.70991400 | 0.74972300 | -1.51893900 |
| H       | -7.88687300 | -1.42390400 | -1.50283600 |

Dispersion correction: -94.06 kcal/mol

B3LYP/6-311+G(2d,2p) energy:
-1.98263437263 a.u.
ZPE: 0.454373 a.u.
Thermal correction to Gibbs Free Energy: 0.385955 a.u.
Dispersion correction: -90.63 kcal/mol

- INT4
- TS1'

B3LYP/6-311+G(2d,2p) energy: -1,982.57191270 a.u.
ZPE: 0.44906 a.u.
Thermal correction to Gibbs Free Energy: 0.382495 a.u.
Dispersion correction: -91.48 kcal/mol

- INT1'

B3LYP/6-311+G(2d,2p) energy: -1,982.58463926 a.u.
ZPE: 0.44906 a.u.
Thermal correction to Gibbs Free Energy: 0.382495 a.u.
Dispersion correction: -91.48 kcal/mol
| Atoms | Coordinates     |
|--------|----------------|
| C      | -4.91383100 -0.30400300 -3.17533500 |
| C      | -2.79966400 -2.80779300 -1.70742000 |
| C      | -2.64400500 -1.78305600 -0.64728000 |
| H      | -4.67204500 2.51805500 -1.29358200 |
| H      | -2.73188400 -3.36918100 0.82974700  |
| C      | -2.64400500 -1.52879600 -0.48585100 |
| N      | -3.61243100 -2.39733700 -2.63690000 |
| C      | -2.90650200 1.25524700 0.34863100  |
| H      | -1.94817500 0.78367200 0.55641300  |
| C      | -3.31207300 2.92968700 2.18120400  |
| H      | -1.29928100 1.34890100 2.97568500  |
| H      | -0.51963000 2.27722000 1.69740000  |
| H      | -0.72592800 3.00587500 3.59986900  |
| O      | -3.00526000 3.90045400 2.76869400  |
| C      | -2.96829000 -1.57550700 1.91548500  |
| N      | -1.82306100 -1.57697100 2.55425500  |
| O      | -0.87218700 -2.45734100 0.72194000  |
| P      | 1.31001800 -0.48668300 0.46391800  |
| O      | 0.03426100 -0.24078800 -0.28697400  |
| C      | 2.74954400 1.62002600 -0.26071000  |
| C      | 3.93019400 1.34711400 -0.85638900  |
| C      | 3.32139000 2.92968700 2.18120400  |
| H      | 4.37353400 1.96344100 2.06017700  |
| H      | 2.44796300 1.09017800 0.30369690  |
| C      | -3.79373000 -0.91983100 2.33200500  |
| N      | -1.23061000 -1.57697100 2.55425500  |
| O      | -0.62687200 -2.78773300 -1.25006200 |
| P      | -1.35837500 0.13693200 -0.15513600 |
| O      | -0.41162100 -0.99880300 -0.15513600 |
| O      | -0.81163900 1.56194700 0.21412100  |
| O      | 2.10118000 -0.26071000 -2.15168000  |
| O      | 1.18118000 0.34863100 0.34863100  |
| O      | 1.22118000 -0.26071000 -2.15168000  |
| O      | 2.78118000 -0.26071000 -2.15168000  |
| O      | 1.96344100 2.06017700 0.30369690  |
| O      | 2.34739700 4.32538700 0.39245600  |
| O      | 2.52786000 -0.23238800 -0.28697400  |
| O      | 1.52286000 0.34863100 0.34863100  |
| O      | 1.63238800 -0.26071000 -2.15168000  |
| O      | 0.62687200 2.78773300 -1.25006200 |
| O      | 2.28507300 -1.90110900 0.27843600  |
| O      | 1.52286000 0.34863100 0.34863100  |
| O      | 1.63238800 -0.26071000 -2.15168000  |
| O      | 0.62687200 2.78773300 -1.25006200 |
| O      | 2.28507300 -1.90110900 0.27843600  |
| O      | 1.63238800 -0.26071000 -2.15168000  |
| O      | 0.62687200 2.78773300 -1.25006200 |
| O      | 2.28507300 -1.90110900 0.27843600  |
### TS3’

**B3LYP/6-311+G(2d,2p) energy:**
-1,982.57798399 a.u.

**ZPE:** 0.445815 a.u.

**Thermal correction to Gibbs Free Energy:** 0.378861 a.u.

**Dispersion correction:** -90.23 kcal/mol

| Atom | x         | y         | z         |
|------|-----------|-----------|-----------|
| C    | -5.543321 | -1.697725 | -0.638235 |
| C    | -4.405872 | -2.475921 | -2.624002 |
| H    | -2.542308 | -1.461831 | -3.073885 |
| C    | -5.485719 | -2.549201 | -1.740212 |
| H    | -6.375522 | -1.769360 | 0.055389  |
| H    | -4.435381 | 2.102315  | 2.448128  |

### INT4’

**B3LYP/6-311+G(2d,2p) energy:**
-1,982.62382726 a.u.

**ZPE:** 0.452367 a.u.

**Thermal correction to Gibbs Free Energy:** 0.380762 a.u.

**Dispersion correction:** -87.41 kcal/mol

| Atom | x         | y         | z         |
|------|-----------|-----------|-----------|
| C    | 2.559330  | 3.797792  | 1.016136  |
| C    | 1.394674  | 3.134989  | 1.732977  |
| H    | 0.853904  | 2.442903  | 1.079360  |
| C    | 1.747246  | 2.558311  | 2.594872  |
| H    | 0.708938  | 3.909880  | 2.077923  |
| O    | 2.626563  | 5.024222  | 0.935708  |
| C    | 1.839424  | -1.087075 | -0.410610 |
| H    | 1.182797  | -1.674008 | -1.055229 |
| H    | 1.603548  | -0.041246 | -0.626136 |
| C    | 1.469542  | -1.344325 | 1.064618  |
| H    | 2.147183  | -0.925415 | 1.805737  |
| N    | 1.204235  | -2.653268 | 1.441536  |
| O    | 1.570990  | -3.158667 | 2.486127  |
| O    | 0.446343  | -3.425374 | 0.645176  |
| P    | -1.801534 | -0.761970 | 0.184776  |
| O    | -0.808680 | -0.085893 | 1.159503  |
| O    | -1.326801 | -2.056810 | -0.438350 |
| O    | -2.200377 | 0.221610  | -1.034651 |
| O    | -3.171303 | -0.882248 | 1.036316  |
| C    | -2.959978 | 1.378784  | -0.810932 |
| C    | -4.327171 | 1.270213  | -0.506814 |
| C    | -2.333479 | 2.607623  | -0.994962 |
| C    | -5.052625 | 2.469305  | -0.392267 |
| C    | -3.079347 | 3.779975  | -0.876023 |
| H    | -1.277306 | 2.628996  | -1.240709 |
| C    | -4.441743 | 3.708301  | -0.574789 |
| H    | -6.106942 | 2.419552  | -0.139236 |
| C    | -2.596825 | 4.741787  | -1.017449 |
| H    | -5.027185 | 4.617610  | -0.474319 |
| C    | -4.398444 | -1.090386 | 0.389645  |
| C    | -5.026346 | -2.318379 | 0.574313  |
| C    | -4.993020 | -0.042927 | -0.333450 |
| H    | -6.291976 | -2.527527 | 0.027324  |
| H    | -4.522879 | -3.086027 | 1.151854  |
| C    | -6.268492 | -0.284011 | -0.873898 |
| C    | -6.912795 | -1.506808 | -0.697054 |
| H    | -6.786727 | -3.482935 | 0.166834  |
| H    | -6.746639 | 0.499114  | -1.453740 |
| H    | -7.895202 | -1.664824 | -1.130598 |
| Atom | X-Cartesian Coordinates | Y-Cartesian Coordinates | Z-Cartesian Coordinates |
|------|-------------------------|-------------------------|-------------------------|
| H    | -0.86757300             | -1.73446400             | 0.34791600              |
| C    | 5.27608700              | -2.12243500             | -1.17136600             |
| C    | 4.59889300              | -0.96104600             | -0.68691400             |
| C    | 5.38199900              | 0.18547400              | -0.35817500             |
| C    | 6.77461800              | -0.91083000             | -0.51443800             |
| H    | -1.06982300             | -0.98458900             | 0.07583000              |
| C    | 6.66201200              | -2.19648800             | -1.32437400             |
| C    | 3.08281000              | -2.57102800             | -1.17097000             |
| C    | 3.18619100              | -1.27915200             | 0.07041400              |
| H    | 7.91313700              | 0.93783500              | -0.23232100             |
| C    | 8.48536800              | 0.10896160              | -1.68984000             |
| C    | 4.51015600              | -3.96609000             | 1.82374900              |
| C    | 2.19485400              | -3.16522200             | -1.33815500             |
| H    | 6.77461800              | 0.09108300              | -1.68984000             |
| C    | 3.08281000              | -2.57102800             | -1.17097000             |
| C    | 3.18619100              | -1.27915200             | 0.07041400              |
| H    | 7.91313700              | 0.93783500              | -0.23232100             |
| C    | 8.48536800              | 0.10896160              | -1.68984000             |
| C    | 4.51015600              | -3.96609000             | 1.82374900              |
| C    | 2.19485400              | -3.16522200             | -1.33815500             |
| H    | 6.77461800              | 0.09108300              | -1.68984000             |
| C    | 3.08281000              | -2.57102800             | -1.17097000             |
| C    | 3.18619100              | -1.27915200             | 0.07041400              |
| H    | 7.91313700              | 0.93783500              | -0.23232100             |
| C    | 8.48536800              | 0.10896160              | -1.68984000             |
| C    | 4.51015600              | -3.96609000             | 1.82374900              |
| C    | 2.19485400              | -3.16522200             | -1.33815500             |
| H    | 6.77461800              | 0.09108300              | -1.68984000             |
| C    | 3.08281000              | -2.57102800             | -1.17097000             |
| C    | 3.18619100              | -1.27915200             | 0.07041400              |
| H    | 7.91313700              | 0.93783500              | -0.23232100             |

B3LYP/6-311+G(2d,2p) energy:

-877.294814288 a.u.

ZPE: 0.262879 a.u.

Thermal correction to Gibbs Free Energy: 0.217794 a.u.

Dispersion correction: -46.45 kcal/mol
B3LYP/6-311+G(2d,2p) energy:
-877.2864919800 a.u.
ZPE: 0.261171 a.u.
Thermal correction to Gibbs Free Energy: 0.213902 a.u.
Dispersion correction: -43.36 kcal/mol

C     3.10729000   -0.21643900    0.00482600
C     1.69529900   -0.10674300    0.19102800
C     1.09672200    1.18097300    0.06253000
C     1.93497400    2.26393600   -0.24532900
C     3.31848400    2.11729600   -0.42326600
C     3.92757700    0.87297500   -0.29805300
C     2.31876700   -2.26756300    0.43797600
C     1.21374200   -1.44537800    0.46214900
H     1.50332300    3.25726700   -0.31038200
H     3.92198500    2.99155200   -0.64651200
H     4.99877300    0.75039000   -0.42554300
H     4.38328900   -1.91517500    0.10260700
N     3.45010900   -1.53973000    0.16988800
C    -0.33748300    1.38986100    0.27705700
H    -0.83484400    0.66955000    0.91970800
C    -1.08228800    2.39218800   -0.24010900
H    -0.64943700    3.11839400   -0.92386400
C    -2.51639500   -0.92389400    0.92386400
C    -3.24998600   -1.91517500    1.02607000
H    -3.18421400    0.64844900    0.96342000
H    -2.81740700    1.77377400    2.00839600
H    -4.29803400    1.99808200    1.03982700
O    -3.10283200    3.53825000   -0.52332000
C    -0.18646300   -1.95205300    0.67871600
H    -0.13768100   -2.97771500    1.05891700
H    -0.72931400   -1.36833300    1.42698900
C    -0.99006500   -1.95548800   -0.63218500
H    -0.55918100   -2.61649400   -1.38175800
N    -2.39708700   -2.44132300   -0.40791200
O    -2.81824900   -3.34044200   -1.12946100
O    -3.04741700   -1.90629600    0.49099400
H    -1.09486500   -0.94860500   -1.04380800

TS3cis

B3LYP/6-311+G(2d,2p) energy:
-1,982.5908302200 a.u.
ZPE: 0.45020 a.u.
Thermal correction to Gibbs Free Energy: 0.387819 a.u.
Dispersion correction: -94.64 kcal/mol

P    -1.51299400   -0.54858900   -0.35396300
O    -0.86856000   -1.63066300    0.45891700
O    -0.64860800    0.28643900   -1.33547200
H     0.27320800    0.73469300   -1.01994900
O    -2.65419500   -1.07928900   -0.37728900
O    -2.34042700    0.41275200    0.65583000
C    -3.92037900   -1.45184300   -0.91775700
C    -4.82790500   -0.47260700   -0.47411100
C    -4.27412800   -2.79459200   -1.02074800
C    -6.12147800   -0.90614400   -0.13401700
C    -5.56533800   -3.19435800   -0.67793100
C    -3.53740300   -3.50456400   -1.38098400
C    -6.49059400   -2.24610300   -0.23481700
C    -6.83738700   -0.17547100    0.22938800
C    -5.84418600   -4.24039100   -0.75693900
C    -7.49597300   -2.54976800    0.03942200
C    -3.22155800   -1.37004000    0.14540400
C    -2.86534100    2.71054800    0.25799300
C    -4.45832400    0.96060400   -0.37997700
C    -3.76553900    3.69189900   -0.15599300
C    -1.89458900    2.95850400    0.67391000
C    -5.34457200    1.97206000   -0.79011600
C    -5.00702600    3.31982700   -0.67924300
C    -3.49676200    4.74021400   -0.07207000
C    -6.30191000    1.68852500   -1.21628200
C    -5.70957800    4.07876800   -1.00896100
C    -5.56380700   -0.59888500   -1.59581200
C    -4.76632000   -0.04397600   -0.55485600
C    -4.11997100   -0.90699400    0.36267500
C    -4.28210700   -2.28031800    0.18671800
C    -5.09611100   -2.80620300   -0.83555900
C    -5.75018000   -1.97718400   -1.74104100
C    -5.50782400    1.63388400   -1.85472100
C    -4.73790800    1.37420300   -0.74519600
C    -3.79567000   -2.96071900    0.87852100
C    -5.21149300   -3.88285300   -0.91556400
C    -6.37006000   -2.38401300   -2.53462700
-1,982.5951714900 a.u.

ZPE: 0.449916 a.u.

Thermal correction to Gibbs Free Energy: 0.386415 a.u.

Dispersion correction: -94.66 kcal/mol

P     -1.82864900   -0.75508000   -0.00342600
O     -1.47097000   -1.87503700    0.94019600
O     -0.76639600   -0.38150900   -1.05731500
H      0.36747100   -0.87785100   -0.82164600
O     -3.16633400   -1.01110600   -0.89046600
O     -4.42912700   -1.01512500   -0.28981300
O     -5.00766000   -0.89232000   -0.12639200
C     -5.11089300   -2.22682300    0.28981300
H     -5.11089300   -2.22682300    0.28981300
H     -4.42912700   -1.01512500   -0.28981300
H     -3.16633400   -1.01110600   -0.89046600
N     -3.28721000   -0.83049500   -0.69749400
C     -0.38613500   -0.83049500   -1.05731500
C     -1.59286000   -0.83049500   -0.69749400
C     -2.82325800   -0.83049500   -0.69749400
C     -4.42912700   -1.01512500   -0.28981300
C     -5.00766000   -0.89232000   -0.12639200
H     -5.11089300   -2.22682300    0.28981300
H     -5.11089300   -2.22682300    0.28981300
H     -4.42912700   -1.01512500   -0.28981300
H     -3.16633400   -1.01110600   -0.89046600
N     -3.28721000   -0.83049500   -0.69749400
C     -0.38613500   -0.83049500   -1.05731500
C     -1.59286000   -0.83049500   -0.69749400
C     -2.82325800   -0.83049500   -0.69749400
C     -4.42912700   -1.01512500   -0.28981300
C     -5.00766000   -0.89232000   -0.12639200
H     -5.11089300   -2.22682300    0.28981300
H     -5.11089300   -2.22682300    0.28981300
H     -4.42912700   -1.01512500   -0.28981300
H     -3.16633400   -1.01110600   -0.89046600

 cis-4

B3LYP/6-311+G(2d,2p) energy: -877.2949781220 a.u.
ZPE: 0.262863 a.u.
Thermal correction to Gibbs Free Energy: 0.217635 a.u.
Dispersion correction: -46.08 kcal/mol

Methyl (E)-3-(1H-indol-4-yl)acrylate (1b)

B3LYP/6-311+G(2d,2p) energy: -669.317542740 a.u.
ZPE: 0.206267 a.u.
Thermal correction to Gibbs Free Energy: 0.164432 a.u.
Dispersion correction: -31.25 kcal/mol
C  4.69721000  1.42448400  0.00431200
H  4.58862200  2.50861700  0.00946800
H  5.24205700  1.09328100  0.89181400
H  5.23992000  1.10154500 -0.88753700
- INT2ester

B3LYP/6-311+G(2d,2p) energy:
-2.057.8681330600 a.u.
ZPE: 0.456375 a.u.
Thermal correction to Gibbs Free Energy: 0.389158
a.u.
Dispersion correction: -95.49 kcal/mol

H  -0.88442600  -2.09589400  -1.71962200
C  -3.17102200  3.19840700   0.46055900
C  -3.18735300  1.77758500   0.32473100
C  -2.61566600  0.99443700   1.36705600
C  -2.05677200  1.66181700   2.46670100
C  -2.06704700  3.06202900   2.57109000
C  -2.62594000  3.85110200   1.57002400
C  -4.10669500  2.70581600  -1.51542000
C  -3.78531600  1.48836800  -0.95917700
H  -1.64076600  1.07420700   3.27919100
H  -1.64086100  3.53320600   3.45114700
H  -2.63922700  4.93413600  -1.64571400
C  -3.86588600  4.71186500  -0.86293900
H  -4.56883800  2.91655300  -2.49738300
H  -0.69254400  2.74191700  -1.04227800
N  -3.75052100  3.72906400  -0.69942400
C  -2.61322900  4.66089000  -1.29775100
H  -3.46587200  -0.94312500  0.82365600
C  -1.61734700  -1.26883900  1.73354700
H  -0.69100000  -0.86680700  2.12998800
C  -1.63897300  -2.71456300  1.50646100
O  -0.61161400  -3.40455800  1.39438100
C  -4.02840600  0.15946800  -1.62771100
H  -4.52008400  0.34119900  -2.59419500
H  -4.73302800  -0.46261300  -1.06236700
C  -2.77325300  -0.63796200  -1.83831000
H  -1.80093600  -0.18339700  -1.96632300
N  -2.83381800  -1.94373900  -1.83967800
O  -1.64898400  -2.68564500  -1.96750700
O  -3.85868800  -2.65718300  -1.73592600
P  1.54415000  -1.17354900  -0.29849400
O  0.42993800  -1.17448300  -1.29033900
O  1.58572400  -2.31376100  0.77193030
O  1.64200500  0.16575400  0.60804100
O  2.95762200  -1.21056700  -1.07238600
C  2.04144100  1.37506300  0.02200000

- TS3ester

B3LYP/6-311+G(2d,2p) energy:
-2.057.8357778600 a.u.
ZPE: 0.455468 a.u.
Thermal correction to Gibbs Free Energy: 0.391497
a.u.
Dispersion correction: -97.66 kcal/mol

H  -0.16527300  -1.62553000  -1.47182500
C  -3.68195800  3.00156600  0.64122000
C  -3.47705900  1.64380000  0.28718800
C  -2.79496800  0.76500400  1.15503200
C  -2.30696200  1.29846800  2.35283500
C  -2.52559900  2.64932400  2.69338400
C  -3.21686700  3.51992400  1.88555700
C  -4.51860200  2.65845000  -1.42342800
C  -4.00365900  1.44594100  -1.02774800
H  -1.78911200  0.65178500  3.05391300
H  -2.14984500  3.01630500  3.64581400
H  -3.37962800  4.55731500  2.13156000
H  -4.61367600  4.55969100  -0.47396000
H  -4.99639700  2.94141800  -2.35082600
H  0.33084200  -3.04899000  1.18828100

S55
- TS3'ester

\[ \text{B3LYP/6-311+G(2d,2p) energy: } -2.0578340608900 \text{ a.u.} \]

\[ \text{ZPE: 0.45153 a.u.} \]

\[ \text{Thermal correction to Gibbs Free Energy: 0.383638 a.u.} \]

\[ \text{Dispersion correction: -91.33 kcal/mol} \]
|   | X     | Y     | Z     |   | X     | Y     | Z     |
|---|-------|-------|-------|---|-------|-------|-------|
| C | -6.27072600 | -0.41045100 | -0.90735600 | H | -6.73238300 | 0.33212200 | -1.55043500 |
| C | -6.93852200 | -1.60289700 | -0.63598600 | H | -7.92236000 | -1.77702100 | -1.05999700 |
| H | -6.85309900 | -3.50502500 | 0.38478900   |   |       |       |       |
Copies of the $^1$H and $^{13}$C NMR spectra

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EI53.

Sample: s857
File: /home/torii/Spettri/Hallic/EI53.caratterizzazioni.protons.fid

Pulse Sequence: 2pul
Solvent: cdcl3
Temp: 25.0 °C / 298.1 K
Operator: ricil
File: EI53.caratterizzazioni.protoni

Bal. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 2.731 sec
Width 3438.8 Hz
3c repetitions
SNR 1500

Data Processing
Line broadening 6.5 Hz
FT size 4K
Total time 37 min. 3 sec

---

EI53.caratterizzazioni.carbonio
Sample: s857
File: /home/torii/Spettri/Hallic/EI53.caratterizzazioni.carbonio.fid

Pulse Sequence: 2pul
Solvent: cdcl3
Temp: 25.0 °C / 298.1 K
Operator: ricil
File: EI53.caratterizzazioni.carbonio

Bal. delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.380 sec
Width 2416.4 Hz
481 repetitions
SNR 1500

Power 41 dB
continuously on

Data Processing
Baseline correction -0.0 Hz
FT size 5K
Total time 4 Ks, 47 min. 14 sec

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S59

Pulse Sequence: alpy1

Solvent: dch2

Temp. 25.0 C / 298.1 K

Sample: 1mL

Fils. 3767.8ms

Spectrum: 600 MHz

Helen; Decay 1.000 sec

Pulse 45.6 degrees

Acq. Time 2.725 sec

Choice 4356.6 Hz

9500 repeatitions

Choice 4250 MHz

Power 45.0W

continuously on

Data Set 12, 36400 MHz

DATA PROCESSING

One broadening 0.1 Hz

Pt file 05258

Total time 2.35 hr, 38 min, 3 sec.
S156_proton
Sample: 5MPrClareto
File: home/schi/Spettro/Spettro/Somminist/S156_proton.six

Pulse Sequence: sigrp
Solvent: orb 3
Temp. 295.0 C / 294.1 K
Operator: riz01
File: S156_proton
Nucleus: 400MHz "m400"

Repr. 3X 339.3245789 MHz
DATA PROCESSING
FT size 0512
Total time 37 min. 3 sec

S150_carbamic
Sample: S304
File: home/schi/Spettro/Spettro/Somminist/S150_carbamic.six

Pulse Sequence: sigrp
Solvent: orb 3
Temp. 295.0 C / 294.1 K
Operator: riz01
File: S150_carbamic
Nucleus: 400MHz "m400"

Repr. 3X 339.3245789 MHz
DATA PROCESSING
FT size 0512
Total time 3 hr. 24 min. 34 sec
Solvent: Acetone
Temp. 30.0 C / 303.1 K
 operator: Junasei
File: NACOA-233A-protonal2c
INosta-000

Relax. delay 1.000 sec
Pulse 45.0 degrees
Arg. time 2.990 sec
Width 3631.9 Hz
16 repetitions
OBSERVE H1. 599.7306975 MHz
DATA PROCESSING
PT size 65536
Total time 1 min. 11 sec

233A Loura00-Triple H1-alpul-odul13 May 29 2014
Solvent: Acetone
Temp. 30.0 C / 303.1 K
operator: Junasei
File: 233A-carbonio-lungo
INosta-000

Relax. delay 4.000 sec
Pulse 51.0 degrees
Arg. time 1.000 sec
Width 36382.7 Hz
16000 repetitions
OBSERVE C13. 350.8021442 MHz
SNOWRIDE H1. 599.7307560 MHz
Power 39 dB
continuously on
WAUDE-16 modulated
DATA PROCESSING
Line broadening 0.6 Hz
Exp. time 1.000 sec
Shifted by -2.100 sec
PT size 133672
Total time 22 hr, 16 min, 49 sec
Copies of the HPLC traces
\[
\text{MeO}_2C \quad \text{NO}_2
\]

rac-3b

3b (dr 87:13)
[from decarboxylation of 3n]
