Synergistic Catalysis: Asymmetric Synthesis of Cyclopentanes bearing 4 Stereogenic Centers.

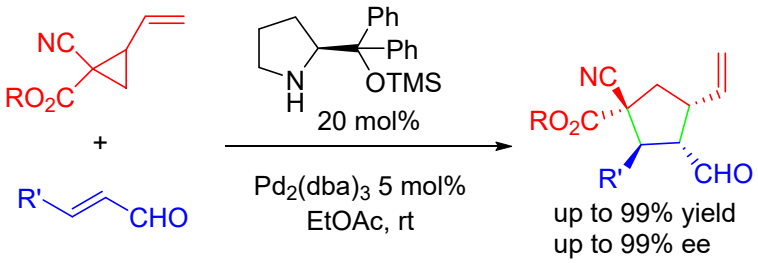
Kaiheng Zhang[a]
Marta Meazza[a]
Anabel Izaga[a,b]
Clotilde Contamine[a,c]
M. Concepción Gimeno[b]
Raquel P. Herrera[d]
Ramon Rios*[a]

[a] School of Chemistry
University of Southampton, Highfield Campus, SO17 1BJ, UK.
E-mail: rrt1f11@soton.ac.uk
Homepage: www.riosresearchgroup.com.

[b] Departamento de Química Inorgánica. Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza. E-50009 Zaragoza, Spain.

[c] Engineering University of CAEN. Ensicaen, 6, boulevard Maréchal Juin CS 45053 14050 CAEN, France.

[d] Laboratorio de Organocatálisis Asimétrica, Departamento de Química Orgánica. Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza. E-50009 Zaragoza, Spain.



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Abstract In this work we present a formal [3+2] cycloaddition based on synergistic catalysis. Vinylcyclopropanes derived from cyanoesters reacts with enals by dual activation using Pd(0) and secondary amines to form the cyclopentanes in good yields and stereoselectivities.

Key words Synergistic catalysis, Organocatalysis, Cyclopentanes, Asymmetric synthesis, Cycloaddition

Synergistic catalysis[1] has become an important alternative to the classic organometallic or organocatalytic chemistry to develop new processes with high efficiency and stereoselectivity.

Synergistic catalysis consists in two catalytic cycles, involving two separate catalysts, that work in a concerted fashion to create a single new bond. The advantages of synergistic catalysis are clear; in the classic catalysis, one single catalyst is used to activate an "unreactive" compound A that reacts with a highly reactive compound B to render C. However, in synergistic catalysis can be used two "unreactive compounds" activated by a catalyst, each one increasing the chemical diversity of the reaction and allowing the discovery of new reactions.

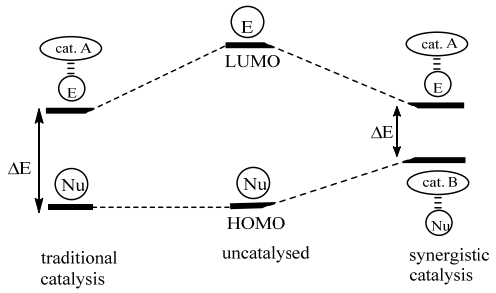
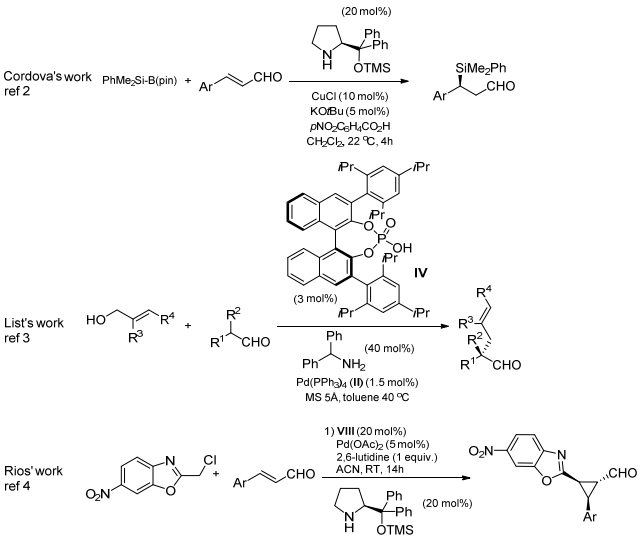


Figure 1: Energy diagram

Despite in Nature synergistic catalysis is a common activation in biological processes, very few advances have been done in organic chemistry since the last decade. Significant progresses have been made lately, for example the initial works of Cordova in β-sylilation, β-arylation or β-borylation,[2] of List in allylation and Overman rearrangements[3] and our recent works in the enantioselective synthesis of benzoxazoles derivatives.[4]



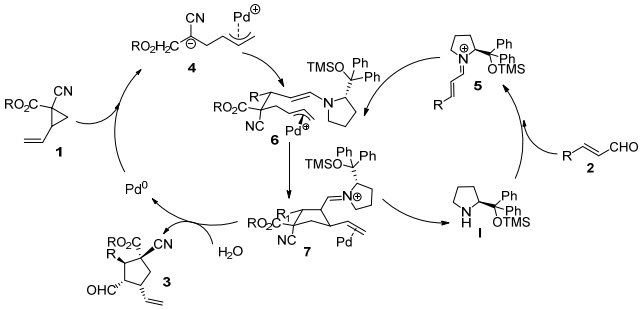
Scheme 1: Previous works

Despite the advantages related to the use of two unreactive substrates, synergistic catalysis can be limited in terms of: possible autoquenching of the catalysts, kinetic issues regarding the concentration of catalytic species or, in terms of atom economy, making one single bond using two catalysts is less efficient than the classic monocatalyst activation.

The first limitation can be easily overcome by carefully choosing the pair of catalysts while the kinetic issues can be avoided thanks to the decrease of the energy activation of the reaction that must be higher than the decrease of the concentration of the active species. Finally, the third limitation could be the most difficult to overcome, because is inherent to the process. Thinking about how we can make the process more efficient, we decided to focus our attention on the development of new processes that contain 2 consecutive reactions (cascade/domino), both of them using the synergistic catalysis approach taking profit of the richness of metal chemistry and the cheap and easy stereo-prediction of secondary amine catalysis.[5]

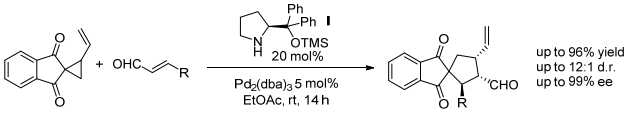
One possible approach to generate a double synergistic cascade reaction consist in the use of vinyl cyclopropanes reaction in a formal [3+2] cycloaddition with enals using a metal activation for the opening of the vinyl cyclopropane and a secondary amine catalyst for the activation of the enal. Several research groups reported similar reactions, almost at the same time, showing the popularity and high competition of this field.[6]

The proposed mechanism can be shown in Scheme 2: in the presence of palladium complex the vinylcyclopropane **1** is cleaved by oxidative addition of the palladium[7] and the corresponding zwitterionic π-allylpalladium intermediate **4** is generated. On the other hand, the enal reacts with the chiral secondary amine **I** to form the iminium ion intermediate **5**. The carbon anion of the dipole **4** acts as a nucleophile through a Michael addition to the iminium intermediate leading to an enolate intermediate **6** (first synergistic catalytic cycle). Next the enamine intermediate reacts intramolecularly with the previously generated allylic palladium *via* a 5-*exo-trig* cyclization furnishing, after protonation and reductive elimination of the Pd complex and hydrolysis of the iminium intermediate, the final cyclopentane compound **7** with the release of the catalysts, thus completing the catalytic cycle. Remarkably, the stereoselectivity of the reaction is perfectly controlled by the chiral secondary amine that blocks one of the faces of the iminium and enamine intermediates. The *cis* configuration between the allyl group and the aldehyde can be explained by the cyclic transition state proposed in Scheme 2. In order to avoid steric interaction, the Pd of the allyl complex will be located on the opposite face respect to the enamine substituent. The proposed mechanism is in agreement with the previously reported ones in similar organocascade reactions.[8]



Scheme 2: Proposed mechanism

In our previous work, we showed our initial studies of the reaction of vinyl cyclopropanes with enals with excellent results (Scheme 3).[4] We proved that Pd(0) catalysts can coexist with the secondary amine activation to generate cyclopentanes in excellent yields and stereoselectivities.

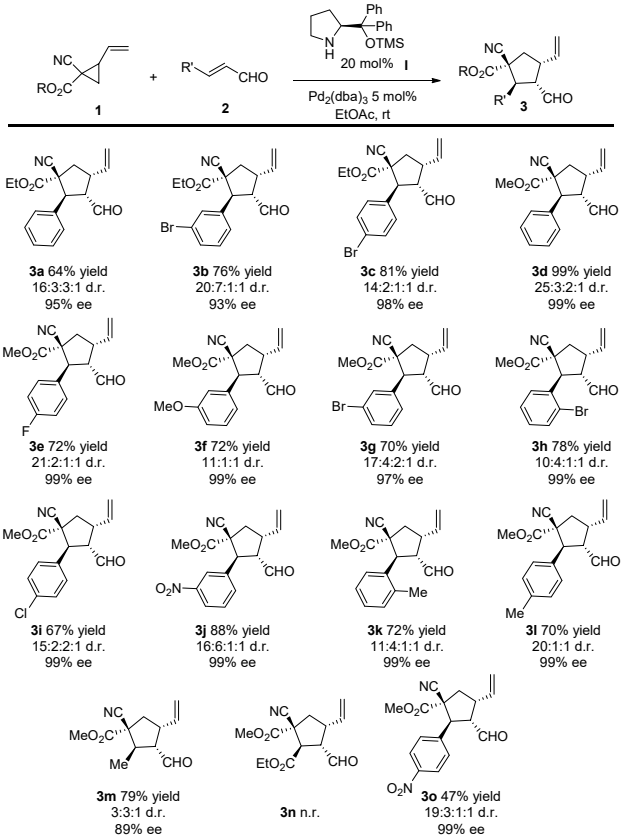


Scheme 3: Previous results

Spurred by these results we wanted to push the boundaries of the reaction: we can generate 4 stereocenters if instead of using symmetric diketovinylcyclopropanes we use cyanoesters derivatives **1**. The advantage of using cyano esters is not only the generation of a new stereocenter but also the possibility to generate highly functionalized cyclic aminoacid derivatives.

After a short reaction screening we found that the best conditions were EtOAc as a solvent, Jørgensen-Hayashi catalyst 20 mol%, $Pd_2(dba)_3$ 5 mol% at room temperature.

With the best conditions on hand we decided to study the scope of the reaction in terms of the enals and cyanoesters (Scheme 4).



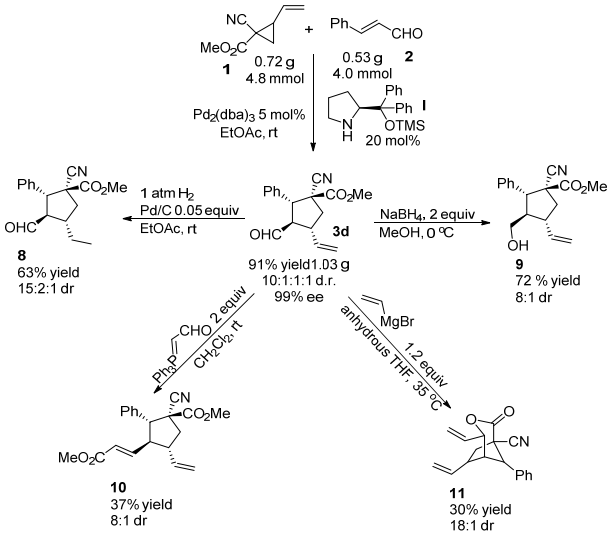
Scheme 4: Scope of the reaction

As shown in Scheme 4, the substituent in the ester is important in terms of stereo selectivity, for example when ethyl ester is used the diastereoselectivity of the reaction decreases as well as the enantioselectivity (**3a** and **3b**). The reaction of the methyl ester with aromatic enals gives the final compounds with excellent diastereo- and enantioselectivities and with good to excellent yields. When substituents where placed in the *ortho* position (**3h** and **3k**) the diastereoselectivity of the reaction decreases but the enantioselectivity remains excellent. The

reaction tolerates different substitution in the aromatic ring like halides (**3b**, **3c**, **3e**, **3g**, **3h** and **3i**) in *ortho*, *meta* and *para* position in good yields and excellent diastereo- and enantioselectivities despite the presence of Pd(0) catalyst. The reaction also tolerates electron-withdrawing groups such as NO_2 (**3j** and **3o**) or electron-donating substituents such as OMe or Me (**3f**, **3k** and **3l**) affording the final products in moderate to good yields and good to excellent diastereo- and enantioselectivities. The only limitation of the present methodology is the use of aliphatic enals, that affords the final compounds in good yields and good enantioselectivities but almost no diastereoselectivity (**3m**). Unfortunately, when the enal derived from glyoxilate was used, the reaction gave complex mixtures and was impossible to isolate any product (**3n**).

The relative and absolute configuration of the compounds were determined by comparison with the literature data and it is in concordance with the proposed mechanism.[9]

We decided to explore the synthetic potential of the present reaction (Scheme 5). First, we demonstrated the possibility to reproduce the reaction in a 4 mmol scale, achieving similar results to the one obtained in a small scale.



Scheme 5: Derivatizations

As it is shown in Scheme 5, several derivatizations have been done to show the applicability of the present reaction. Remarkably in almost all the examples the diastereoselectivity of the reaction did not change. Surprisingly, when product **3d** was treated with a Grignard reagent, the resulting product was obtained in low yields but excellent diastereoselectivity, moreover the final product is the result of the Grignard addition to the aldehyde followed by and intramolecular cyclization to render the fused bicyclic product **11**.

In conclusion, we have developed a new cascade reaction based on synergistic catalysis. Vinyl cyclopropanes bearing cyano esters groups react with enals through Pd and secondary amine catalysis, rendering the highly functionalized cyclopentanes bearing 4 stereocenters in good yields and diastereoselectivities and excellent enantioselectivities.

The experimental section has no title; please leave this line here.

Thin layer chromatography (TLC) was performed on Merck TLC Silicagel 60 F254. Product spots were visualized by UV-light at 254 nm. Column chromatography was effectuated using silica gel (Geduran Si60, 40-63 μm). Melting points were measured with a Gallenkamp Electrothermal apparatus and are uncorrected. Infra-red spectra were recorded on a Nicolet 380 FT-IR; the IR analysis were performed with the compounds dissolved in $CHCl_3$. ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR, 2D-NMR were recorded with a Bruker DPX400 NMR. High resolution mass spectra were recorded using a MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a Time of Flight (TOF) analyser. Optical rotations were performed on an Optical Activity PolAAr 2001 machine. The HPLC analysis were performed on a Perkin Elmer Flexar HPLC and an Agilent 1220 Infinity LC system HPLC. Note: the racemates for the HPLC analysis were prepared mixing the product obtained with the *S* and *R* catalysts.

General synergistic catalysis procedure

In a closed vial were added the secondary amine catalyst 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine **I** (0.04 mmol, 0.2 equiv), vinylcyclopropane **1** (0.24 mmol, 1.2 equiv), enal **2** (0.2 mmol, 1 equiv), $Pd_2(dba)_3$ (0.01 mmol, 0.05 equiv) and EtOAc (1 ml). The reaction was stirred at room temperature for 16 h. After completion, the mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc/*n*-hexane) to afford the desired product **4**.

Ethyl 1-cyano-3-formyl-2-phenyl-4-vinylcyclopentane-1-carboxylate (3a)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 64% (0.128 mmol, 38 mg), dr was calculated based on crude NMR, dr: 16:3:3:1.

IR (CH_2Cl_2 liquid film): 2982, 1734, 1453, 1368, 1238, 1096, 930, 728, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.5 Hz, 1H), 7.25 (ddd, *J* = 7.3, 4.0, 2.4 Hz, 5H), 5.71 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.22 (d, *J* = 16.9 Hz, 1H), 5.14 (d, *J* = 10.1 Hz, 1H), 4.22 (d, *J* = 10.1 Hz, 1H), 4.14 (dd, *J* = 7.1, 2.4 Hz, 2H), 3.71 – 3.60 (m, 2H), 2.55 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.33 – 2.24 (m, 1H), 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 167.6, 135.4, 135.1, 128.7, 128.6, 128.2, 118.5, 117.9, 63.2, 57.2, 55.3, 52.4, 43.6, 43.0, 14.0.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=17.6 min, t_{major}=23.5 min. 95% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{18}H_{19}NKO_3$ $[M+K]^+$: 336.1205, found: 336.1206.

$[\alpha]_D^{22}$ =+11.9º (c=0.9 in $CHCl_3$) (*R* catalyst)

Ethyl 1-cyano-3-formyl-2-(3-bromophenyl)-4-vinylcyclopentane-1-carboxylate (3b)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 76% (0.152 mmol, 57 mg), dr was calculated based on crude NMR, dr: 20:7:1:1.

IR (CH_2Cl_2 liquid film): 2982, 1734, 1595, 1567, 1477, 1431, 1236, 1076, 930, 855, 790, 471 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.6 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.17 (ddd, *J* = 12.2, 10.7, 6.8 Hz, 3H), 5.75 – 5.64 (m, 1H), 5.24 (d, *J* = 16.9 Hz, 1H), 5.15 (d, *J* = 9.9 Hz, 1H), 4.18 (tdd, *J* = 7.1, 6.4, 2.4 Hz, 3H), 3.86 – 3.72 (m, 1H), 3.64 – 3.59 (m, 1H), 2.59 – 2.51 (m, 1H), 2.30 – 2.21 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 167.3, 137.5, 135.2, 131.7, 131.6, 130.3, 126.6, 122.8, 118.9, 117.6, 63.4, 57.0, 55.1, 51.6, 43.4, 42.9, 14.0.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=17.9 min, t_{major}=24.0 min. 93% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{18}H_{19}BrNNaO_3$ $[M+Na]^+$: 398.0371, found: 398.0362.

$[\alpha]_D^{22}$ =+3.3º (c=1.7 in $CHCl_3$) (*R* catalyst)

Ethyl 2-(4-bromophenyl)-1-cyano-3-formyl-4-vinylcyclopentane-1-carboxylate (3c)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 81% (0.162 mmol, 61 mg), dr was calculated based on the NMR of the crude. dr: 14:2:1:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.3 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 5.80-5.70 (m, 1H), 5.30 (d, *J* = 16.9 Hz, 1H), 5.21 (d, *J* = 9.9 Hz, 1H), 4.30-4.20 (m, 3H), 3.80-3.65 (m, 2H), 2.66 (dd, *J* = 13.3, 6.8 Hz, 1H), 2.34 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 167.3, 135.2, 134.2, 132.4, 131.9, 131.9, 129.9, 129.8, 129.6, 122.7, 118.7, 117.7, 63.4, 57.2, 55.0, 51.5, 43.4, 43.0, 14.0.

HPLC analysis with Chiralpak AY-H column (hexane/*i*PrOH = 95:5, flow rate 1.0 mL/min, λ = 220 nm): t_r = 17.5 min, 26.9 min; 98% ee.

HRMS *m/z* (ESI+) Exact mass calculated for $C_{18}H_{19}Br_{79}NO_3$ $[M+H]^+$: 376.0543, found: 376.0548.

$[\alpha]_D^{23}$ = -104° (c = 0.6, $CHCl_3$) (*S* catalyst)

Methyl 1-cyano-3-formyl-2-phenyl-4-vinylcyclopentane-1-carboxylate (3d)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 99% (0.19 mmol, 56 mg), dr was calculated based on crude NMR, dr: 25:3:2:1.

IR (CH_2Cl_2 liquid film): 2968, 1754, 1439, 1435, 1255, 1098, 730, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.5 Hz, 1H), 7.36 – 7.30 (m, 5H), 5.79 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.30 (d, *J* = 16.9 Hz, 1H), 5.22 (d, *J* = 10.0 Hz, 1H), 4.31 (d, *J* = 10.1 Hz, 1H), 3.76 (s, 3H), 3.71 dd, *J* = 8.7, 2.4 Hz, 2H), 2.64 (dd, *J* = 13.2, 6.9 Hz, 1H), 2.35 (dd, *J* = 13.3, 9.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 168.1, 135.3, 135.0, 128.8, 128.6, 128.1, 118.6, 117.8, 57.1, 55.3, 53.8, 52.4, 43.6, 43.1.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=23.6 min, t_{major}=23.6 min. >99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1281, found: 284.1288.

$[\alpha]_D^{22}$ =-31.0° (c=3.5 in $CHCl_3$) (*S* catalyst)

Methyl 1-cyano-3-formyl-2-(4-fluorophenyl)-4-vinylcyclopentane-1-carboxylate (3e)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 72% (0.144 mmol, 43 mg), dr was calculated based on crude NMR, dr: 21:2:1:1.

IR (CH_2Cl_2 liquid film): 2958, 1742, 1604, 1512, 1436, 1241, 1162, 1015, 930, 842, 802, 707, 568 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.5 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 5.76 (ddd, *J* = 16.9, 10.0, 8.5 Hz, 1H), 5.30 (d, *J* = 16.9 Hz, 1H), 5.22 (d, *J* = 9.9 Hz, 1H), 4.29 (d, *J* = 10.1 Hz, 1H), 3.76 (s, 3H), 3.73 – 3.64 (m, 2H), 2.67 – 2.60 (m, 1H), 2.32 (dd, *J* = 14.0, 10.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.9, 168.0, 135.2, 130.8, 129.9, 129.8, 118.7, 115.9, 115.7, 57.2, 55.2, 53.8, 51.6, 43.4, 43.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.35.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=14.1 min, t_{major}=17.1 min. 99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{16}FNO_3$ $[M+H]^+$: 302.1103, found: 302.1105.

$[\alpha]_D^{22}$ =+59.0° (c=1.0 in $CHCl_3$) (*R* catalyst)

Methyl 1-cyano-3-formyl-2-(3-methoxylphenyl)-4-vinylcyclopentane-1-carboxylate (3f)

The reaction was performed following the general procedure, obtaining yellow solid. Yield: 72% (0.144 mmol, 45 mg), dr was calculated based on crude NMR, dr: 11:1:1. mp: 115-126 °C.

IR (CH_2Cl_2 liquid film): 2954, 2837, 1739, 1601, 1584, 1492, 1435, 1246, 1162, 930, 874, 789 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.7 Hz, 1H), 7.23 – 7.18 (m, 1H), 6.89 – 6.79 (m, 3H), 5.80 – 5.68 (m, 1H), 5.26 (d, *J* = 16.9 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.24 (d, *J* = 10.1 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.71 – 3.60 (m, 2H), 2.64 – 2.55 (m, 1H), 2.30 (dd, *J* = 13.3, 9.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 168.1, 159.8, 136.5, 135.3, 129.8, 120.3, 118.7, 114.1, 114.0, 113.9, 57.0, 55.2, 55.2, 53.8, 52.4, 43.6, 43.2.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{major}=35.2 min, t_{minor}=42.3 min. >99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{18}H_{19}N_2NaO_4$ $[M+Na]^+$: 336.1203, found: 336.1206.

$[\alpha]_D^{22}$ =-9.4° (c=1.2 in $CHCl_3$) (S catalyst)

Methyl 1-cyano-3-formyl-2-(3-bromophenyl)-4-vinylcyclopentane-1-carboxylate (3g)

The reaction was performed following the general procedure, obtaining a yellow solid. Yield: 70% (0.14 mmol, 51 mg), dr was calculated based on crude NMR, dr: 17:4:2:1. mp: 109-113 °C.

IR (CH_2Cl_2 liquid film): 2954, 1740, 1722, 1595, 1568, 1473, 1433, 1249, 1024, 930, 752, 544 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, *J* = 1.2 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.22 – 7.14 (m, 2H), 5.68 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.24 (d, *J* = 16.9 Hz, 1H), 5.15 (d, *J* = 9.7 Hz, 1H), 4.19 (d, *J* = 10.0 Hz, 1H), 3.72 (s, 3H), 3.67 – 3.56 (m, 2H), 2.57 (dd, *J* = 13.3, 6.9 Hz, 1H), 2.25 (dd, *J* = 13.4, 9.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 167.8, 137.5, 135.1, 131.8, 131.4, 130.4, 126.7, 122.8, 118.9, 117.5, 56.9, 55.0, 53.9, 51.6, 43.5, 43.1.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=22.9 min, t_{major}=31.0 min. 97% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{16}BrNNaO_3$ $[M+Na]^+$: 384.0200, found: 384.0206.

$[\alpha]_D^{22}$ =+12.3° (c=1.4 in $CHCl_3$) (*R* catalyst)

Methyl 1-cyano-3-formyl-2-(2-bromophenyl)-4-vinylcyclopentane-1-carboxylate (3h)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 78% (0.156 mmol, 56 mg), dr was calculated based on crude NMR, dr: 10:4:1:1.

IR (CH_2Cl_2 liquid film): 2954, 2848, 1744, 1722, 1473, 1434, 1248, 1103, 931, 753, 573 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.7 Hz, 1H), 7.57 (td, *J* = 8.1, 1.4 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.17 (td, *J* = 7.8, 1.6 Hz, 1H), 5.86 (ddd, *J* = 17.0, 10.1, 8.6 Hz, 1H), 5.33 (d, *J* = 16.9 Hz, 1H), 5.24 (d, *J* = 10.0 Hz, 1H), 4.85 (d, *J* = 9.3 Hz, 1H), 3.78 (s, 3H), 3.72 – 3.56 (m, 2H), 3.37 – 3.16 (m, 1H), 2.61 (dd, *J* = 13.3, 9.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 167.3, 135.0, 135.0, 133.2, 129.9, 129.1, 127.9, 125.9, 118.7, 118.0, 59.7, 54.1, 52.6, 50.4, 43.9, 42.1.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{16}BrNNaO_3$ $[M+Na]^+$: 384.0215, found: 384.0206.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{major}=25.2 min, t_{minor}=35.7 min. >99% ee.

$[\alpha]_D^{22}$ =-18.8° (c=0.6 in $CHCl_3$) (*S* catalyst)

Methyl 1-cyano-3-formyl-2-(4-chlorophenyl)-4-vinylcyclopentane-1-carboxylate (3i)

The reaction was performed following the general procedure, obtaining a white solid. Yield: 67% (0.134 mmol, 43 mg), dr was calculated based on crude NMR, dr: 15:2:2:1. mp: 115-123 °C.

IR (CH_2Cl_2 liquid film): 2955, 1740, 1439, 1435, 1416, 1248, 1092, 928, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (t, *J* = 4.1 Hz, 1H), 7.35 – 7.02 (m, 5H), 5.75 – 5.62 (m, 1H), 5.23 (dd, *J* = 16.9, 3.2 Hz, 1H), 5.18 – 5.10 (m, 1H), 4.26 – 4.16 (m, 1H), 3.70 (s, 3H), 3.59 (ddd, *J* = 12.3, 10.2, 3.7 Hz, 2H), 2.57 (dd, *J* = 13.3, 7.0 Hz, 1H), 2.25 (dd, *J* = 13.3, 9.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.8, 167.9, 135.1, 134.6, 133.6, 129.5, 129.1, 118.8, 117.6, 57.1, 55.0, 53.9, 51.6, 43.4, 43.1.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=15.1 min, t_{major}=35.2 min. 99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{16}ClNNaO_3$ $[M+Na]^+$: 340.0708, found: 340.0711.

$[\alpha]_D^{22}$ =+18.8° (c=1.1 in $CHCl_3$) (*R* catalyst)

Methyl 1-cyano-3-formyl-2-(3-nitrophenyl)-4-vinylcyclopentane-1-carboxylate (3j)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 88% (0.176 mmol, 58 mg), dr was calculated based on crude NMR, dr: 16:6:1:1.

IR (CH_2Cl_2 liquid film): 2957, 1742, 1604, 1512, 1436, 1241, 1162, 1015, 930, 842, 802 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.7 Hz, 1H), 8.25 – 8.16 (m, 2H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.55 (td, *J* = 7.8, 3.4 Hz, 1H), 5.81 – 5.71 (m, 1H), 5.35 (dd, *J* = 16.9, 5.6 Hz, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 4.46 – 4.40 (m, 1H), 3.84 – 3.79 (m, 3H), 3.79 – 3.71 (m, 2H), 2.73 – 2.67 (m, 1H), 2.38 – 2.30 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.27, 167.55, 148.5, 137.5, 134.8, 134.3, 129.9, 123.6, 123.4, 119.2, 117.3, 57.0, 54.8, 54.1, 51.1, 43.3, 43.0.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=12.6 min, t_{major}=30.4 min. >99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{16}N_2NaO_5$ $[M+Na]^+$: 351.0960, found: 351.0951.

$[\alpha]_D^{22}$ =+7.0° (c=1.5 in $CHCl_3$) (*R* catalyst)

Methyl 1-cyano-3-formyl-2-(2-methylphenyl)-4-vinylcyclopentane-1-carboxylate (3k)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 72% (0.144 mmol, 43 mg), dr was calculated based on crude NMR, dr: 11:4:1:1.

IR (CH_2Cl_2 liquid film): 2967, 1752, 1640, 1595, 1568, 1473, 1433, 1249, 1024, 930, 755 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 1.4 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.24 – 7.14 (m, 2H), 5.86 – 5.73 (m, 1H), 5.33 (d, *J* = 16.9 Hz, 1H), 5.22 (dd, *J* = 6.6, 3.7 Hz, 1H), 4.63 (d, *J* = 9.6 Hz, 1H), 3.74 (s, 3H), 3.69 – 3.61 (m, 1H), 2.60 (dt, *J* = 9.8, 4.9 Hz, 1H), 2.48 – 2.38 (m, 2H), 2.37 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.2, 168.4, 137.4, 135.2, 134.0, 130.7, 128.1, 127.3, 126.4, 118.6, 117.5, 59.9, 53.8, 47.2, 44.1, 43.4, 19.5.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=97.5:2.5, flow rate=1.0ml/min, 210nm); t_{minor}=20.8 min, t_{major}=29.3 min. >99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{18}H_{19}NNaO_3$ $[M+Na]^+$: 320.1253, found: 320.1257.

$[\alpha]_D^{22}$ =+2.3° (c=1.2 in $CHCl_3$) (*R* catalyst)

Methyl 1-cyano-3-formyl-2-(4-methylphenyl)-4-vinylcyclopentane-1-carboxylate (3l)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 70% (0.14 mmol, 42 mg), dr was calculated based on crude NMR, dr: 20:1:1.

IR (CH_2Cl_2 liquid film): 3082, 2955, 2849, 1742, 1720, 1641, 1530, 1436, 1351, 1251, 1000, 931, 839 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 1.6 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.08 – 7.04 (m, 2H), 5.77 – 5.65 (m, 1H), 5.21 (d, *J* = 16.9 Hz, 1H), 5.13 (dd, *J* = 10.0, 0.7 Hz, 1H), 4.19 (d, *J* = 10.1 Hz, 1H), 3.68 (s, 3H), 3.64 – 3.54 (m, 2H), 2.60 – 2.51 (m, 1H), 2.30 (ddd, *J* = 10.2, 7.4, 3.9 Hz, 1H), 2.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.3, 168.2, 138.4, 135.4, 131.9, 129.6, 128.0, 118.5, 117.9, 57.1, 55.4, 53.7, 52.2, 43.6, 43.1, 21.1.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=19.9 min, t_{major}=31.7 min. >99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{18}H_{19}KNO_3$ $[M+K]^+$: 336.1001, found: 336.0997.

$[\alpha]_D^{22}$ =+19.9° (c=1.0 in $CHCl_3$) (*R* catalyst)

Methyl 1-cyano-3-formyl-2-methyl-4-vinylcyclopentane-1-carboxylate (3m)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 79% (0.158 mmol, 35 mg), dr was calculated based on crude NMR, dr: 3:3:1.

IR (CH_2Cl_2 liquid film): 2957, 1738, 1641, 1436, 1386, 1247, 924 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 8.4 Hz, 1H), 5.70 (dt, *J* = 19.0, 9.5 Hz, 1H), 5.23 – 5.10 (m, 2H), 3.90 – 3.86 (m, 3H), 3.11 – 2.94 (m, 2H), 2.58 (dddd, *J* = 35.0, 23.3, 13.8, 8.6 Hz, 2H), 2.28 – 2.17 (m, 1H), 1.33 – 1.22 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 168.3, 135.6, 119.6, 118.2, 59.2, 53.8, 46.2, 43.8, 42.4, 42.2, 15.3.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=95:5, flow rate=1.0ml/min, 210nm); t_{minor}=23.6 min, t_{major}=23.6 min. 89% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{12}H_{15}NNaO_3$ $[M+Na]^+$: 244.0942, found: 244.0944.

$[\alpha]_D^{22}$ =+12.1° (c=0.7 in $CHCl_3$) (*R* catalyst)

Methyl 1-cyano-3-formyl-2-(4-nitrophenyl)-4-vinylcyclopentane-1-carboxylate (3o)

The reaction was performed following the general procedure, obtaining a yellow oil. Yield: 47% (0.94 mmol, 31 mg), dr was calculated based on crude NMR, dr: 19:3:1:1.

IR (CH_2Cl_2 liquid film): 2955, 2849, 1743, 1721, 1605, 1435, 1349, 1252, 1014, 932, 738, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.6 Hz, 1H), 8.21 – 8.18 (m, 2H), 7.58 – 7.50 (m, 2H), 5.75 (ddd, *J* = 16.8, 9.8, 5.2 Hz, 1H), 5.33 (dd, *J* = 16.8, 4.2 Hz, 1H), 5.25 (dd, *J* = 9.9, 3.7 Hz, 1H), 4.40 (d, *J* = 10.0 Hz, 1H), 3.78 (s, 3H), 3.77 – 3.69 (m, 2H), 2.73 – 2.65 (m, 1H), 2.35 – 2.28 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.3, 167.5, 148.0, 142.6, 134.8, 129.4, 124.0, 119.2, 117.3, 57.2, 54.7, 54.1, 51.2, 43.3, 43.2.

HPLC analysis with Chiralpak AY-H column (EA/iPrOH=70:30, flow rate=1.0ml/min, 210nm); t_{minor}=14.7 min, t_{major}=39.2 min. >99% ee.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{17}N_2O_5$ $[M+H]^+$: 329.1121, found: 329.1132.

$[\alpha]_D^{22}$ =+38.0° (c=1.0 in $CHCl_3$) (*R* catalyst)

General procedure of hydrogenation with H_2

To a two-neck round-bottom flask, **3d** (0.2 mmol, 1 equiv) and Pd/C (0.01 mmol, 0.05 equiv) were added to EtOAc (1 ml). The RBF was sealed and the air was removed *in vacuo* and filled with H_2 twice. The reaction was stirred at room temperature overnight, filtered through celite, washed with EtOAc and concentrated *in vacuo*. The crude hydrogenated product was purified by column chromatography (EtOAc:hexane=1:5).

Methyl-1-cyano-4-ethyl-3-formyl-2-phenylcyclopentane-1-carboxylate (8)

The reaction was performed following the general procedure, obtaining a colorless oil in 63% yield (0.126 mmol, 36 mg).

IR (CH_2Cl_2 liquid film): 2958, 1738, 1605, 1520, 1451, 1346, 1268, 1154, 733, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (d, *J* = 2.3 Hz, 1H), 7.30 – 7.25 (m, 5H), 4.22 (d, *J* = 10.4 Hz, 1H), 3.69 (s, 3H), 3.58 (td, *J* = 10.6, 2.3 Hz, 1H), 2.88 (ddd, *J* = 21.7, 10.9, 5.8 Hz, 1H), 2.58 (dd, *J* = 12.9, 6.8 Hz, 1H), 2.06 (dd, *J* = 13.0, 11.0 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.41 – 1.30 (m, 1H), 0.93 (dd, *J* = 8.7, 6.0 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 168.3, 135.4, 128.8, 128.5, 128.2, 118.0, 56.6, 55.3, 53.7, 52.7, 43.6, 42.3, 24.7, 12.7.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{19}NNaO_3$ $[M+Na]^+$: 308.1263, found: 308.1257.

General procedure for the reduction with $NaBH_4$

To a vial, **3d** (0.14 mmol, 1 equiv) was dissolved in 2 ml of MeOH at 0 °C then sodium borohydride (0.21 mmol, 1.5 equiv) was added. The stirring mixture was monitored by TLC analysis. Saturated ammonium chloride solvent was added to quench reaction. The solution was extracted with EtOAc and the organic layers were dried over anhydrous magnesium sulfate, concentrated *in vacuo* and purified by column chromatography (EtOAc: hexane=1:3) to afford the alcohol product **9**.

Methyl-1-cyano-3-(hydroxymethyl)-2-phenyl-4-vinylcyclopentane-1-carboxylate (9)

The reaction was performed following the general procedure, obtaining a colorless oil in 72% yield (0.101 mmol, 29 mg).

IR (CH_2Cl_2 liquid film): 3384, 2930, 2878, 1715, 1640, 1495, 1250, 1068, 734, 702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 5H), 6.00 (ddd, *J* = 17.1, 10.1, 9.0 Hz, 1H), 5.18 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.14 (dd, *J* = 10.2, 0.8 Hz, 1H), 3.65 (s, 3H), 3.60 (d, *J* = 11.7 Hz, 1H), 3.52 (t, *J* = 4.9 Hz, 2H), 3.33 – 3.22 (m, 1H), 2.89 – 2.78 (m, 1H), 2.56 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.29 (dd, *J* = 13.3, 9.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 137.6, 135.6, 128.8, 128.5, 128.4, 118.4, 117.5, 61.1, 55.4, 54.9, 53.6, 47.7, 43.0, 42.9.

HRMS m/z (ESI+) Exact mass calculated for $C_{17}H_{19}NNaO_3$ $[M+Na]^+$: 308.1263, found: 308.1257.

General procedure for the Wittig reaction

To a small vial, the aldehyde (0.2 mmol, 1 equiv) and methyl triphenylphosphoranylidene acetate (0.4 mmol, 2 equiv), were added to CH_2Cl_2 (2 ml). Then, the mixture was stirred at room temperature overnight. After completion, the solution was evaporated *in vacuo* and the crude product was purified by flash column chromatography (EtOAc: hexane=1:2).

Methyl 1-cyano-3-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)-2-phenyl-4-vinylcyclopentane-1-carboxylate (10)

The reaction was performed following the general procedure, obtaining a yellow oil in 37% yield (0.074 mmol, 25 mg).

IR (CH_2Cl_2 liquid film): 2952, 1738, 1718, 1655, 1497, 1434, 1254, 1169, 1137, 982, 920, 721, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 5H), 6.69 (dd, *J* = 15.7, 8.7 Hz, 1H), 5.74 (ddd, *J* = 16.7, 10.5, 8.7 Hz, 1H), 5.60 (dd, *J* = 15.7, 1.0 Hz, 1H), 5.12 – 5.08 (m, 1H), 5.05 (dd, *J* = 5.4, 4.3 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 4H), 3.54 – 3.46 (m, 1H), 3.36 – 3.24 (m, 1H), 2.65 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.35 (dd, *J* = 13.7, 8.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 166.1, 146.0, 136.7, 134.5, 128.8, 128.6, 128.2, 123.3, 118.1, 117.4, 57.2, 55.7, 53.7, 51.5, 48.2, 44.8, 42.7.

HRMS m/z (ESI+) Exact mass calculated for $C_{20}H_{21}NNaO_4$ $[M+Na]^+$: 362.1365, found: 362.1363.

General procedure for the Grignard reaction

To an oven-dried round-bottom flask, **3d** (0.176 mmol, 1 equiv) was dissolved in THF (1.76 ml) and stirred for 10 min under nitrogen at 0 °C. To this mixture, vinylmagnesium chloride (0.211 mmol, 1.2 equiv) was slowly added. The reaction was allowed to warm up to rt, then was heated at 35 °C overnight. Upon completion, the reaction was quenched with saturated aqueous ammonium chloride solution and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude was purified by column chromatography (EtOAc:hexane=1:5).

2-oxo-8-phenyl-4,6-divinyl-3-oxabicyclo[3.2.1]octane-1-carbonitrile (11)

The reaction was performed following the general procedure, obtaining a colorless oil in 30% yield (0.053 mmol, 15 mg).

IR (CH_2Cl_2 liquid film): 2969, 2878, 1740, 1640, 1210, 1126, 728, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.39 (m, 2H), 7.35 (dd, *J* = 7.1, 4.8 Hz, 3H), 5.92 – 5.79 (m, 2H), 5.50 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.45 (dd, *J* = 11.0, 1.5 Hz, 1H), 5.30 (d, *J* = 10.3 Hz, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.17 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 1H), 3.39 (dd, *J* = 11.8, 6.6 Hz, 1H), 2.82 (dd, *J* = 14.6, 11.4 Hz, 1H), 2.62 (d, *J* = 6.4 Hz, 1H), 2.39 (dd, *J* = 14.7, 5.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 135.6, 135.3, 134.7, 129.1, 128.2, 127.5, 119.4, 118.4, 116.3, 79.6, 50.2, 49.6, 47.8, 41.0, 38.9.

HRMS m/z (ESI+) Exact mass calculated for $C_{18}H_{17}NNaO_2$ $[M+Na]^+$: 302.1147, found: 302.1151.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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