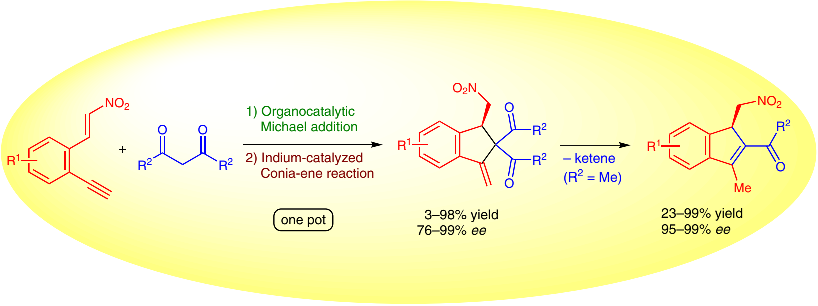
Enantioselective Catalytic One-Pot Synthesis of Functionalized Methyleneindanes and Methylindenes via a Michael/Conia-Ene Sequence

Arne R. Philipps
Marcus Blümel
Simon Dochain
Daniel Hack
Dieter Enders*

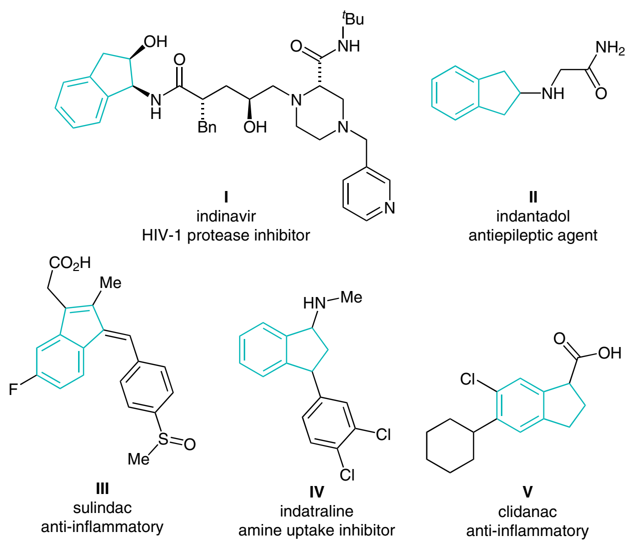
Institute of Organic Chemistry, RWTH Aachen University,
Landoltweg 1, 52074 Aachen, Germany
enders@rwth-aachen.de



Received: 09.11.2016
Accepted after revision: 11.11.2016
Published online: 06.12.2016
DOI: 10.1055/s-0036-1588113; Art ID: ss-2016-z0789-op

Abstract An enantioselective one-pot Michael addition/Conia-ene reaction sequence catalyzed by the combination of a squaramide and indium(III) triflate has been developed. Employing 2-ethynyl-β-nitrostyrenes and 1,3-dicarbonyl compounds as substrates, the functionalized methyleneindanes and methylindenes are obtained in good to excellent enantiomeric excesses. For the indane/indene conversion a concerted fragmentation is proposed.

Key words organocatalysis, indium catalysis, Conia-ene reaction, indanes, indenes



I
indinavir
HIV-1 protease inhibitor

II
indantadol
antiepileptic agent

III
sulindac
anti-inflammatory

IV
indatraline
amine uptake inhibitor

V
clidanac
anti-inflammatory

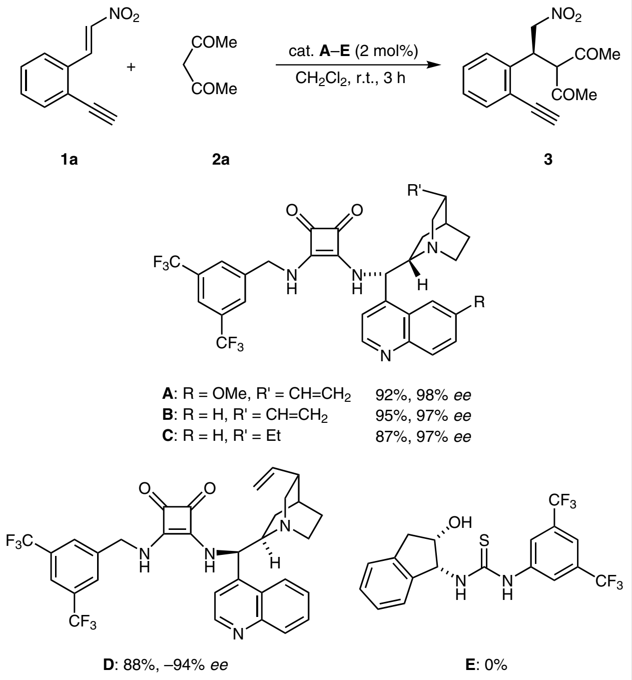
Figure 1 Examples of indane and indene pharmaceuticals

The importance of the indane and indene scaffolds in pharmaceutical chemistry cannot be overstated.[1] There are numerous examples of successfully implemented molecules and the scope of their bioactivity is far reaching and broad.[2,3] In Figure 1 the structures of indinavir (**I**), an HIV-1 protease inhibitor,[4] indantadol (**II**), an antiepileptic agent,[5] the nonsteroidal anti-inflammatory drug sulindac (**III**),[6] the amine uptake inhibitor indatraline (**IV**),[7] and the anti-inflammatory drug clidanac (**V**)[8] are given as typical examples of bioactive indanes and indenes. At the same time, these scaffolds have gained enormous importance in materials science.[9,10]

Recently, there has been a lot of growth in the research field of organocatalysis in combination with transition-metal catalysis,[11] enabling a large number of new accessible transformations. Our group showed the possibility of exploiting the versatile reactivity of 2-ethynyl-β-nitrostyrenes **1** to form tetracyclic indole derivatives[12] and spiropyrazolones[13] using either gold or silver salts as the metal catalyst. In particular, the Conia-ene reaction is an efficient tool which offers an easy, straightforward, and atom-economical approach towards cyclopentanes and cyclohexanes, as well as their heterocyclic counterparts.[14] Due to its great synthetic potential, the combination of organocatalysis with the Conia-ene reaction has been the topic of several investigations. There are novel opportunities for the introduction of stereoinformation into various important target molecules.[13,15] In addition to the mentioned Conia-ene reactions, there have been further reports on the combination of organocatalysis and indium catalysis for various transformations, such as the α-alkylation of aldehydes,[16] allylation reactions,[17] 1,2/1,4-additions to enones,[18] and hetero-Diels–Alder reactions.[19]

To the best of our knowledge, there is only one example of an asymmetric organocatalysis/Conia-ene sequence, employing an indium salt as the metal catalyst, precedent in the literature.[15c] In contrast to our envisioned protocol, which leads to compounds bearing a stereocenter at the β-position to the dicarbonyl moiety, the reported procedure gives rise to cyclopentanes that feature the stereocenter at the α-position. Herein, we present a novel catalytic sequence utilizing an enantioselective organocatalytic Michael addition of dicarbonyl compounds **2** to 2-ethynyl-β-nitrostyrenes **1** and a subsequent cyclization via a Conia-ene reaction with an indium catalyst. This protocol allows for a direct one-pot access to methyleneindanes or methylindenes, depending on the nature of the dicarbonyl compound **2**.[20]

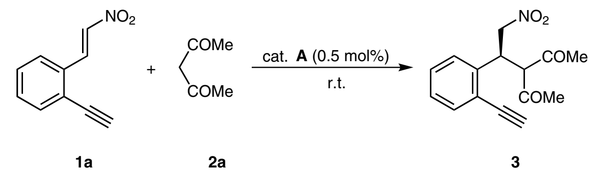
Initially, we focused on the enantioselective Michael addition and thus treated 2-ethynyl-β-nitrostyrene (**1a**) with acetylacetone (**2a**) in the presence of different squaramide and thiourea catalysts in dichloromethane (Scheme 1).[21] While the thiourea catalyst **E** did not show any catalytic activity in this reaction, all of the tested squaramide catalysts showed very satisfying results. This might be due to the tertiary amine moiety, which the tested thiourea catalyst does not bear, assisting in deprotonation of the nucleophile. Catalyst **A** derived from quinine showed the best asymmetric induction with 98% *ee* and an excellent yield of 92%.



Scheme 1 Catalyst screening for the Michael reaction

In the next step, the choice of solvent was investigated using a reduced amount of catalyst **A** of only 0.5 mol% (Table 1). The results in dichloromethane and chloroform were quite similar but, surprisingly, the lower catalyst loading had a beneficial effect on the stereoselectivity of this reaction. This may be due to a competing side reaction with higher catalyst loading. In toluene and in diethyl ether the reaction did not proceed as smoothly as in the chlorinated solvents and gave only mediocre yields. Overall, the choice of solvent did not have a stark influence on the asymmetric induction, as all isolated products had an enantiomeric excess of at least 98% *ee*.

Table 1 Optimization of the Reaction Conditions for the Michael Addition[a]



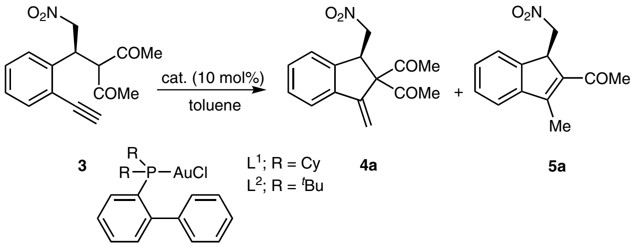
Entry	Solvent	Time (h)	Yield (%)[b]	*ee* (%)[c]
1[d]	CH_2Cl_2	3	92	98
2	CH_2Cl_2	2	90	≥99
3	$CHCl_3$	3	93	≥99
4	toluene	3	44	99
5	Et_2O	3	52	≥99

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.33 mmol), **A** (0.5 mol%), solvent (1.5 mL).
[b] Yield of the isolated product **3**.
[c] Determined by HPLC on a chiral stationary phase.
[d] 2 mol% of **A** was used.

In order to optimize the conditions for the Conia-ene cyclization of the Michael adduct **3** to form the methyleneindane **4a**, several metal salts were investigated (Table 2). The selection of metal sources was based on prior reports in the literature of their successful application in similar Conia-ene reactions.[22] While 10 mol% of $AgNTf_2$ in toluene showed no catalytic activity, all of the tested gold sources led to decomposition of the starting material (entries 1–4). Irrespective of the phosphine ligand and the solvent, the reaction was very torpid and gave no isolable product but a complex mixture of compounds. When copper(I) chloride in chloroform was used no reaction was observed, even when the temperature was raised to 50 °C (entry 5). Zinc(II) chloride showed some reactivity, but after 24 hours at 80 °C only a trace amount of **4a** could be isolated (entry 6). Increasing the temperature to 100 °C for an hour did not improve the results.

With indium(III) triflate in toluene at 80 °C, complete conversion was achieved after 3 hours with a surprising result. In addition to the expected methyleneindane **4a**, a second product was isolated and identified as methylindene **5a** (Table 2, entry 7). When iron(III) chloride in chloroform was employed at room temperature, full conversion with a strong preference towards methylindene **5a** was observed after 5 hours and methyleneindane **4a** was only isolated in a small amount (entry 8).

Table 2 Optimization of the Cyclization Reaction[a]



Entry	Catalyst	Time (h)	Temp	Yield (%)[b]	**4a/5a**
1	$AgNTf_2$	120	r.t. to 40 °C	no reaction	–
2	$AgNTf_2/AuL^1$	120	r.t. to 40 °C	decomposition	–
3	$AgNTf_2/AuL^2$	120	r.t. to 40 °C	decomposition	–
4[c]	$AgNTf_2/AuL^1$	120	r.t. to 40 °C	decomposition	–
5[c]	CuCl	120	r.t. to 50 °C	no reaction	–
6	$ZnCl_2$	24	80–100 °C	traces	–
7	$In(OTf)_3$	3	80 °C	99	1.4:1
8[c]	$FeCl_3$	5	r.t.	98	1:15

[a] Reaction conditions: **3** (0.1 mmol), catalyst (10 mol%), solvent (1.0 mL).
[b] Yield of the isolated products.
[c] $CHCl_3$ as solvent.

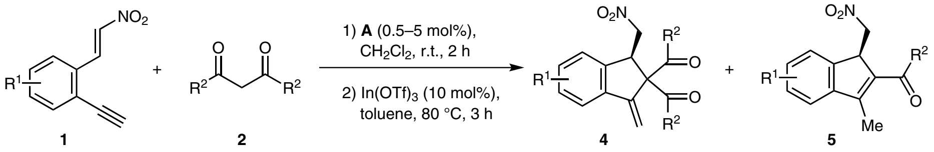
With these optimized conditions in hand, the reaction sequence was combined for a one-pot protocol and the scope of the reaction was explored (Table 3). When the diketone acetylacetone (**2a**) was employed in the reaction with the unsubstituted 2-ethynyl-β-nitrostyrene (**1a**), the yield of methyleneindane **4a** was very good (76%) and a virtually complete stereoselectivity was observed. At the same time, the methylindene **5a** was obtained in 23% yield with an excellent enantioselectivity of 98% *ee*. In an additional attempt to influence the selectivity of this reaction, the temperature during the indium-catalyzed step was increased to 100 °C, but this gave exactly the same result concerning both yield and enantiomeric excess of **4a** and **5a**. For 2-ethynyl-β-nitrostyrenes bearing a halide at the *para*-position to the triple bond, only small amounts of the methyleneindanes **4b** and **4c** were isolated; however, both still exhibited excellent enantiomeric excesses. When chlorine was replaced by fluorine, the yield for the methylindene **5c** was slightly better. Electron-rich arene substrates bearing a methoxy or methylenedioxy moiety gave no methyleneindane; however, the corresponding methylindenes **5d** and **5e** were isolated in good to excellent yields. While the asymmetric induction for **5d** was virtually complete, the stereoselectivity for **5e** was still very good with 95% *ee*. With heptane-3,5-dione (**2**, R^2 = Et) as the diketone compound, only the methylindene **5f** was obtained in a good yield of 60% and an excellent enantiomeric excess of 97%.

In the next step, different malonates were subjected to these reaction conditions. Unfortunately, the catalyst loading of the first step had to be increased to 5 mol% as no reaction with diesters occurred using a lower amount. With all the tested malonates, only the expected methyleneindane **4** was formed (Table 3). The combination of the unsubstituted 2-ethynyl-β-nitrostyrene (**1a**) and dimethyl malonate gave the corresponding indane **4g** in 61% yield and with an excellent enantioselectivity of 95% *ee*. Changing dimethyl malonate to diethyl malonate gave almost identical results with a good yield and excellent *ee* value of **4h**. In addition, several substituents R^1 at the aromatic ring of the nitroolefin, such as chlorine, fluorine, and methoxy, as well as bis(chlorophenyl) malonates, were tolerated and very good enantioselectivities of 76–95% *ee* were reached (**4i–n**).

However, the one-pot Michael/Conia-ene protocol also showed its limitations. Several diketones, such as hexafluoroacetylacetone, dimedone, and indandione, as well as substituted phenylmalonates, sterically demanding malonates (R^2 = O*t*-Bu), and Meldrum's acid, showed no reactivity. When an internal alkyne instead of a terminal alkyne moiety was used, the Michael addition occurred but there was no subsequent cyclization reaction.

To further explore the formation of the unexpected methylindenes and to pursue the presumption of a subsequent process, instead of a competing side reaction, the isolated methyleneindane **4a** was resubjected to the cyclization conditions with iron(III) chloride in chloroform at room temperature. After 5 hours, the methylindene **5a** was

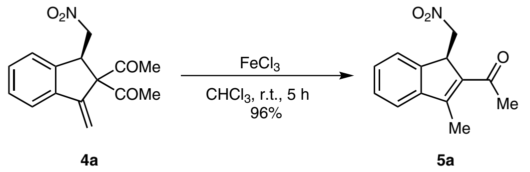
Table 3 Substrate Scope of the Michael/Conia-Ene One-Pot Reaction Sequence[a]



4/5	R^1	R^2	Cat. (mol%)	Yield **4** (%)[b]	*ee* **4** (%)[c]	Yield **5** (%)[b]	*ee* **5** (%)[c]
a	H	Me	0.5	76	99	23	98
b	4-Cl[d]	Me	0.5	3	96	34	98
c	4-F[d]	Me	0.5	7	99	54	98
d	4-OMe[d]	Me	0.5	–	–	99	≥99
e	4,5-OCH_2O[d]	Me	0.5	–	–	69	95
f	H	Et	0.5	–	–	60	97
g	H	OMe	5	61	95	–	–
h	H	OEt	5	61	96	–	–
i	4-OMe[d]	OMe	5	57	95	–	–
j	4-Cl[d]	OMe	5	54	94	–	–
k	4-F[d]	OMe	5	65	82	–	–
l	H	*o*-ClC_6H_4O	5	14	80	–	–
m	H	*m*-ClC_6H_4O	5	25	76	–	–
n	H	*p*-ClC_6H_4O	5	98	86	–	–

[a] Reaction conditions: 0.3-mmol scale using **1** (1.0 equiv), **2** (1.1 equiv), **A** (0.5–5 mol%), CH_2Cl_2 (1.5 mL); $In(OTf)_3$ (10 mol%), toluene (1.5 mL).
[b] Yield of isolated products.
[c] Determined by HPLC on a chiral stationary phase.
[d] Numbering refers to the starting material **1**, with the ethynyl substituent as position 1.

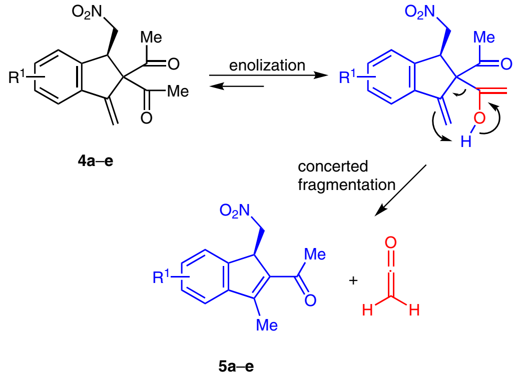
obtained in 96% yield (Scheme 2). Based on this result showing a subsequent, and not a competing, reaction pathway, we postulate a fragmentation mechanism (Scheme 3). After enolization of the methyleneindane ketones **4a**–**e**, a concerted fragmentation reaction occurs with the loss of ketene and the formation of methylindenes **5a**–**e**. This reaction pathway is in agreement with the product selectivity of the malonates, since the corresponding methyleneindanedicarboxylates **4g**–**n** cannot undergo an enolization. Additionally, the product selectivity for the electron-rich arenes with the donor methoxy or methylenedioxy R^1 group at the *para*-position and conjugation with the reacting double bond can be explained, resulting only in the methylindenes **5d** and **5e**.



Scheme 2 Formation of methylindene **5a** starting from methyleneindane **4a**

The proposed fragmentation is supported by HRMS measurements, which showed that in the conversion of **4a** into **5a** the exact mass of ketene was lost. This type of concerted fragmentation has been described previously under basic conditions,[23] and was used by Mander and Woolias on cyclic derivatives.[24]

In conclusion, we have developed a novel one-pot enantioselective synthesis of methyleneindanes and methylindenes in good to excellent enantiomeric excesses (76–99%



Scheme 3 Postulated reaction mechanism for the concerted ketene fragmentation

ee) based on a catalytic Michael/Conia-ene sequence employing 2-ethynyl-β-nitrostyrenes and 1,3-dicarbonyl compounds as substrates. The formation of the methylindenes can be explained by a subsequent concerted fragmentation and loss of ketene.

All commercially available compounds were used without further purification. Analytical TLC was performed using Macherey & Nagel SIL G-25 UV254 silica gel, particle size 0.040–0.063 mm (230–240 mesh, flash). UV irradiation (254 nm) was used to visualize the developed TLC plates. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Finnigan SSQ7000 spectrometer (EI, 70 eV) and HRMS on a Thermo Fisher Scientific Orbitrap XL spectrometer. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 spectrometer using an ATR unit. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury 600 or Inova 400 instruments with TMS as internal standard. Analytical HPLC was performed on an Agilent 1100 or 1260 Series instrument using chiral stationary phases (Chiralpak IC, Chiralpak IA, Chiralpak IB, Chiralpak AS, Chiralcel OD). The nitroalkenes **1** were prepared as described previously,[13] and the phenyl malonates **2l–n** according to the reported procedure.[25] The catalysts **A–D** were synthesized as described earlier.[21c] The absolute configuration of compounds **3**, **4**, and **5** was assigned by comparison with the products obtained in previous work.[21]

(*S*)-3-(1-(2-Ethynylphenyl)-2-nitroethyl)pentane-2,4-dione (3)

A solution of nitroalkene **1a** (52.0 mg, 0.3 mmol), acetylacetone (**2a**; 33.0 mg, 0.33 mmol), and squaramide **A** (1 mg, 0.5 mol%) in $CHCl_3$ (1.5 mL) was stirred at r.t. for 3 h. The crude mixture was directly purified by column chromatography (silica gel, *n*-pentane/Et_2O, 3:1) to afford **3** as a colorless solid; yield: 76 mg (93%); mp 132–134 °C; $[\alpha]_D^{23}$ +285.1 (*c* 1.0, $CHCl_3$); 99% *ee* [HPLC: Chiralpak IC]; R_f = 0.25 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3240, 1709, 1546, 1483, 1446, 1358, 1253, 1143, 955, 774, 715, 676 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (dd, *J* = 7.6, 1.2 Hz, 1 H, CH_{Ar}), 7.30 (td, *J* = 7.6, 1.4 Hz, 1 H, CH_{Ar}), 7.25 (td, *J* = 7.6, 1.2 Hz, 1 H, CH_{Ar}), 7.14 (d, *J* = 7.8 Hz, 1 H, CH_{Ar}), 4.88 (dd, *J* = 12.5, 7.2 Hz, 1 H, C*H*HNO$_2$), 4.80–4.72 (m, 1 H, C*H*CH$_2$), 4.67 (dd, *J* = 12.5, 4.2 Hz, 1 H, CH*H*NO$_2$), 4.64 (d, *J* = 10.1 Hz, 1 H, CHCO), 3.49 (s, 1 H, C≡CH), 2.25 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 202.0, 201.1, 138.0, 134.2, 129.6, 128.2, 127.9, 121.6, 83.7, 80.9, 76.6, 69.2, 40.3, 30.7, 28.6.

MS (EI, 70 eV): *m*/*z* (%) = 273.1 (7) [M]$^+$, 227.2 (11), 183.1 (59), 169.1 (26), 155.2 (29), 141.1 (83), 128.1 (86), 115.1 (100), 102.2 (21), 89.2 (19).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_4Na^+$: 296.0893; found: 296.0898.

Methyleneindanes/Methylindenes 4/5 by Sequential Catalysis; General Procedure

A solution of nitroalkene **1** (0.3 mmol), dicarbonyl compound **2** (0.33 mmol), and squaramide **A** (0.5–5 mol%) in CH_2Cl_2 (1.5 mL) was stirred at r.t. for 2 h. The solvent was evaporated by heating at 50 °C and changed to toluene (1.5 mL). Then In(OTf)$_3$ (10 mol%) was added and the reaction mixture was heated at 80 °C for 3 h before being directly purified by flash column chromatography (silica gel, *n*-pentane/Et_2O, 3:1).

(*R*)-1,1′-(1-Methylene-3-(nitromethyl)-2,3-dihydro-1*H*-indene-2,2-diyl)bis(ethan-1-one) (4a)

Compound **4a** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 62 mg (76%); colorless solid; mp 135–137 °C; $[\alpha]_D^{23}$ +255.9 (*c* 1.0, $CHCl_3$); 99% *ee* [HPLC: Chiralcel OD]; R_f = 0.23 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3399, 2924, 2323, 2090, 1816, 1702, 1553, 1429, 1359, 1183, 1035, 908, 760, 676 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 6.3, 2.2 Hz, 1 H, CH_{Ar}), 7.38–7.29 (m, 2 H, CH_{Ar}), 7.24–7.18 (m, 1 H, CH_{Ar}), 5.96 (d, *J* = 1.0 Hz, 1 H, CH_{ol}), 5.44 (d, *J* = 1.0 Hz, 1 H, CH_{ol}), 4.90 (dd, *J* = 14.4, 7.8 Hz, 1 H, C*H*HNO$_2$), 4.65 (dd, *J* = 14.4, 4.3 Hz, 1 H, CH*H*NO$_2$), 4.59 (dd, *J* = 7.8, 4.3 Hz, 1 H, C*H*CH$_2$), 2.37 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 203.9, 203.4, 145.6, 141.7, 137.6, 130.3, 128.6, 123.6, 121.3, 110.2, 80.8, 75.8, 46.4, 28.2, 27.1.

MS (EI, 70 eV): *m*/*z* (%) = 274.1 (10) [M + H]$^+$, 230.1 (100), 184.1 (76), 169.1 (60).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_4Na^+$: 296.0893; found: 296.0893.

(*R*)-1,1′-(5-Chloro-1-methylene-3-(nitromethyl)-2,3-dihydro-1*H*-indene-2,2-diyl)bis(ethan-1-one) (4b)

Compound **4b** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 3 mg (3%, the major product was **5b**); brownish oil; $[\alpha]_D^{23}$ –122.0 (*c* 0.1, $CHCl_3$); 96% *ee* [HPLC: Chiralpak IC]; R_f = 0.33 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3408, 3283, 2943, 2667, 2325, 2094, 1912, 1705, 1556, 1364, 1188, 1086, 850, 672 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.3 Hz, 1 H, CH_{Ar}), 7.29 (ddd, *J* = 8.2, 1.8, 0.8 Hz, 1 H, CH_{Ar}), 7.23–7.19 (m, 1 H, CH_{Ar}), 5.93 (d, *J* = 1.4 Hz, 1 H, CH_{ol}), 5.47 (d, *J* = 1.4 Hz, 1 H, CH_{ol}), 4.89 (dd, *J* = 14.7, 7.8 Hz, 1 H, C*H*HNO$_2$), 4.62 (dd, *J* = 14.7, 4.1 Hz, 1 H, CH*H*NO$_2$), 4.54 (dd, *J* = 7.8, 4.1 Hz, 1 H, C*H*CH$_2$), 2.37 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 203.4, 203.0, 144.4, 143.4, 136.2, 136.2, 129.1, 124.0, 122.4, 110.8, 80.9, 75.3, 46.0, 28.0, 27.1.

MS (EI, 70 eV): *m*/*z* (%) = 264.1 (99), 218.0 (67), 203.0 (65), 139.0 (100).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}NO_4ClNa^+$: 330.0504; found: 330.0503.

(*R*)-1,1′-(5-Fluoro-1-methylene-3-(nitromethyl)-2,3-dihydro-1*H*-indene-2,2-diyl)bis(ethan-1-one) (4c)

Compound **4c** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 6 mg (7%, the major product was **5c**); colorless oil; $[\alpha]_D^{23}$ –33.0 (*c* 0.1, $CHCl_3$); 99% *ee* [HPLC: Chiralpak IC]; R_f = 0.36 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 2936, 2324, 2095, 1910, 1706, 1555, 1481, 1358, 1189, 889, 677 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 8.5, 5.0 Hz, 1 H, CH_{Ar}), 7.02 (tdd, *J* = 8.6, 2.4, 0.8 Hz, 1 H, CH_{Ar}), 6.94 (ddd, *J* = 8.4, 2.3, 1.0 Hz, 1 H, CH_{Ar}), 5.88 (d, *J* = 0.9 Hz, 1 H, CH_{ol}), 5.42 (d, *J* = 0.4 Hz, 1 H, CH_{ol}), 4.89 (dd, *J* = 14.6, 8.0 Hz, 1 H, C*H*HNO$_2$), 4.63 (dd, *J* = 14.6, 4.1 Hz, 1 H, CH*H*NO$_2$), 4.57–4.48 (m, 1 H, C*H*CH$_2$), 2.38 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 203.6, 203.1, 164.1 (d), 144.4, 144.0 (d), 133.6, 122.9 (d), 116.2 (d), 111.1 (d), 109.8, 81.1, 75.4, 46.1, 28.0, 27.1.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –109.43 (dd, *J* = 13.5, 8.4 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 292.1 (26) [M + H]$^+$, 248.1 (100), 202.1 (73), 187.0 (64).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}NO_4FNa^+$: 314.0799; found: 314.0798.

Dimethyl (*R*)-1-Methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4g)

Compound **4g** was isolated after flash chromatography (*n*-pentane/Et$_2$O, 3:1); yield: 56 mg (61%); colorless solid; mp 88–91 °C; $[\alpha]_D^{23}$ –114.8 (*c* 0.8, CHCl$_3$); 95% *ee* [HPLC: Chiralpak IC]; R_f = 0.50 (*n*-pentane/Et$_2$O, 1:1).

IR (ATR): 3024, 2944, 2642, 2301, 2182, 2006, 1715, 1557, 1435, 1377, 1256, 1039, 909, 781 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.56–7.41 (m, 1 H, CH$_{Ar}$), 7.39–7.24 (m, 2 H, CH$_{Ar}$), 7.24–7.11 (m, 1 H, CH$_{Ar}$), 5.91 (s, 1 H, CH$_{ol}$), 5.61 (s, 1 H, CH$_{ol}$), 4.86 (t, *J* = 6.6 Hz, 1 H, C*H*CH$_2$), 4.77 (dd, *J* = 14.2, 6.4 Hz, 1 H, C*H*HNO$_2$), 4.68 (dd, *J* = 14.2, 6.8 Hz, 1 H, CH*H*NO$_2$), 3.79 (s, 3 H, CH$_3$), 3.73 (s, 3 H, CH$_3$).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 169.0, 168.7, 144.2, 140.5, 138.2, 129.8, 128.8, 123.8, 121.2, 111.1, 76.4, 66.8, 53.5, 53.1, 47.4.

MS (EI, 70 eV): *m*/*z* (%) = 306.2 (9) [M + H]$^+$, 258.1 (78), 230.1 (52), 199.1 (100), 141.2 (81).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_6Na^+$: 328.0792; found: 328.0790.

Diethyl (*R*)-1-Methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4h)

Compound **4h** was isolated after flash chromatography (*n*-pentane/Et$_2$O, 3:1); yield: 61 mg (61%); colorless solid; mp 84–86 °C; $[\alpha]_D^{23}$ –195.5 (*c* 0.5, CHCl$_3$); 96% *ee* [HPLC: Chiralpak IC]; R_f = 0.48 (*n*-pentane/Et$_2$O, 1:1).

IR (ATR): 2982, 1729, 1555, 1455, 1377, 1234, 1042, 886, 763 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.52–7.48 (m, 1 H, CH$_{Ar}$), 7.33–7.27 (m, 2 H, CH$_{Ar}$), 7.22–7.19 (m, 1 H, CH$_{Ar}$), 5.92 (s, 1 H, CH$_{ol}$), 5.63 (s, 1 H, CH$_{ol}$), 4.85–4.79 (m, 2 H, CH$_2$NO$_2$), 4.71 (td, *J* = 9.9, 5.2 Hz, 1 H, C*H*CH$_2$), 4.29–4.12 (m, 4 H, 2 × OCH$_2$), 1.28 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 1.25 (d, *J* = 7.1 Hz, 3 H, CH$_3$).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 168.5, 168.2, 144.2, 140.6, 138.3, 129.8, 128.7, 123.8, 121.2, 111.0, 76.6, 66.8, 62.4, 62.3, 47.3, 13.9, 13.8.

MS (EI, 70 eV): *m*/*z* (%) = 334.1 (16) [M + H]$^+$, 286.1 (100), 258.1 (11), 214.1 (59), 169.1 (63), 141.1 (58).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}NO_6Na^+$: 356.1105; found: 356.1104.

Dimethyl (*R*)-5-Methoxy-1-methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4i)

Compound **4i** was isolated after flash chromatography (*n*-pentane/Et$_2$O, 3:1); yield: 57 mg (57%); colorless oil; $[\alpha]_D^{23}$ –54.0 (*c* 0.1, CHCl$_3$); 95% *ee* [HPLC: Chiralpak IA]; R_f = 0.63 (*n*-pentane/Et$_2$O, 1:1).

IR (ATR): 2955, 1731, 1559, 1440, 1374, 1237, 1081, 904, 827, 726 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.40 (d, *J* = 8.6 Hz, 1 H, CH$_{Ar}$), 6.85 (ddd, *J* = 8.4, 2.3, 0.5 Hz, 1 H, CH$_{Ar}$), 6.69 (d, *J* = 2.2 Hz, 1 H, CH$_{Ar}$), 5.73 (d, *J* = 0.7 Hz, 1 H, CH$_{ol}$), 5.45 (d, *J* = 0.7 Hz, 1 H, CH$_{ol}$), 4.81 (t, *J* = 6.5 Hz, 1 H, C*H*CH$_2$), 4.75 (dd, *J* = 14.2, 6.4 Hz, 1 H, C*H*HNO$_2$), 4.67 (dd, *J* = 14.2, 6.7 Hz, 1 H, CH*H*NO$_2$), 3.79 (s, 3 H, CH$_3$), 3.79 (s, 3 H, CH$_3$), 3.73 (s, 3 H, CH$_3$).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 169.1, 168.7, 161.3, 143.6, 142.2, 131.0, 122.4, 115.7, 108.7, 108.2, 76.4, 67.1, 55.5, 53.5, 53.1, 47.4.

MS (EI, 70 eV): *m*/*z* (%) = 335.6 (3) [M]$^+$, 288.6 (19), 229.5 (36), 185.4 (46), 171.4 (59), 128.3 (100), 115.3 (38), 98.3 (53).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NO_7Na^+$: 358.0897; found: 358.0895.

Dimethyl (*R*)-5-Chloro-1-methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4j)

Compound **4j** was isolated after flash chromatography (*n*-pentane/Et$_2$O, 3:1); yield: 55 mg (54%); colorless solid; mp 100–101 °C; $[\alpha]_D^{23}$ +3.5 (*c* 0.6, CHCl$_3$); 94% *ee* [HPLC: Chiralpak IC]; R_f = 0.58 (*n*-pentane/Et$_2$O, 1:1).

IR (ATR): 2294, 2093, 1724, 1556, 1436, 1376, 1252, 1070, 899, 826, 716 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.42 (d, *J* = 8.3 Hz, 1 H, CH$_{Ar}$), 7.31–7.25 (m, 1 H, CH$_{Ar}$), 7.19 (s, 1 H, CH$_{Ar}$), 5.88 (d, *J* = 0.8 Hz, 1 H, CH$_{ol}$), 5.64 (d, *J* = 0.8 Hz, 1 H, CH$_{ol}$), 4.81 (t, *J* = 6.3 Hz, 1 H, C*H*CH$_2$), 4.77 (dd, *J* = 14.2, 6.0 Hz, 1 H, C*H*HNO$_2$), 4.68 (dd, *J* = 14.2, 6.6 Hz, 1 H, CH*H*NO$_2$), 3.80 (s, 3 H, CH$_3$), 3.74 (s, 3 H, CH$_3$).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 168.7, 168.4, 143.0, 142.1, 136.9, 135.5, 129.2, 124.2, 122.4, 111.8, 76.0, 66.8, 53.6, 53.2, 47.0.

MS (EI, 70 eV): *m*/*z* (%) = 339.0 (33) [M]$^+$, 292.1 (100), 264.0 (51), 233.0 (66).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}NO_6ClNa^+$: 362.0402; found: 362.0393.

Dimethyl (*R*)-5-Fluoro-1-methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4k)

Compound **4k** was isolated after flash chromatography (*n*-pentane/Et$_2$O, 3:1); yield: 63 mg (65%); colorless oil; $[\alpha]_D^{23}$ –4.3 (*c* 0.9, CHCl$_3$); 82% *ee* [HPLC: Chiralpak IC]; R_f = 0.52 (*n*-pentane/Et$_2$O, 1:1).

IR (ATR): 3464, 3283, 2955, 2324, 2097, 1730, 1551, 1436, 1371, 1218, 1071, 916, 832, 690 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.44 (dd, *J* = 8.5, 5.0 Hz, 1 H, CH$_{Ar}$), 6.99 (td, *J* = 8.6, 2.3 Hz, 1 H, CH$_{Ar}$), 6.89 (dd, *J* = 8.5, 2.3 Hz, 1 H, CH$_{Ar}$), 5.81 (s, 1 H, CH$_{ol}$), 5.57 (s, 1 H, CH$_{ol}$), 4.80 (dd, *J* = 12.4, 6.1 Hz, 1 H, C*H*CH$_2$), 4.76 (dd, *J* = 18.5, 5.6 Hz, 1 H, C*H*HNO$_2$), 4.66 (dd, *J* = 13.1, 5.9 Hz, 1 H, CH*H*NO$_2$), 3.78 (s, 3 H, CH$_3$), 3.72 (s, 3 H, CH$_3$).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 168.8, 168.4, 163.8, 142.9, 142.6, 134.3, 122.8, 116.4, 111.1, 110.7, 76.0, 67.0, 53.5, 53.2, 47.1.

^{19}F NMR (376 MHz, CDCl$_3$): δ = –110.47 (s).

MS (EI, 70 eV): *m*/*z* (%) = 323.1 (24) [M]$^+$, 276.1 (100), 248.1 (56), 217.1 (90), 159.1 (53).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}NO_6FNa^+$: 346.0697; found: 346.0699.

Bis(2-chlorophenyl) (*R*)-1-Methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4l)

Compound **4l** was isolated after flash chromatography (*n*-pentane/Et$_2$O, 3:1); yield: 21 mg (14%); yellowish oil; $[\alpha]_D^{23}$ –18.0 (*c* 0.1, CHCl$_3$); 80% *ee* [HPLC: Chiralpak IA]; R_f = 0.32 (*n*-pentane/Et$_2$O, 4:1).

IR (ATR): 3288, 3072, 2925, 2087, 1924, 1756, 1641, 1555, 1474, 1375, 1202, 1056, 1002, 945, 906, 832, 744, 682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61–7.57 (m, 1 H, CH_{Ar}), 7.44 (dt, *J* = 7.8, 1.8 Hz, 2 H, CH_{Ar}), 7.38–7.32 (m, 2 H, CH_{Ar}), 7.29–7.18 (m, 7 H, CH_{Ar}), 6.13 (d, *J* = 1.1 Hz, 1 H, CH_{ol}), 6.00 (d, *J* = 1.0 Hz, 1 H, CH_{ol}), 5.25 (dd, *J* = 14.0, 4.5 Hz, 1 H, C*H*HNO_2), 5.10 (dd, *J* = 7.7, 4.5 Hz, 1 H, C*H*CH_2), 5.02 (dd, *J* = 14.0, 7.7 Hz, 1 H, CH*H*NO_2).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 165.6, 146.5, 146.3, 143.3, 140.3, 138.0, 130.6, 130.5, 130.1, 129.0, 128.0, 127.9, 127.8, 127.7, 126.8, 126.5, 123.9, 123.3, 123.1, 121.4, 112.5, 76.3, 66.9, 47.7.

MS (EI, 70 eV): *m*/*z* (%) = 450.1 (10), 295.1 (43), 231.1 (53), 214.1 (100), 168.1 (36).

HRMS (ESI): *m*/*z* $[M + K]^+$ calcd for $C_{25}H_{17}NO_6Cl_2K^+$: 536.0065; found: 536.0064.

Bis(3-chlorophenyl) (*R*)-1-Methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4m)

Compound **4m** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 37 mg (25%); yellowish oil; $[\alpha]_D^{23}$ –48.3 (*c* 1.0, $CHCl_3$); 76% *ee* [HPLC: Chiralpak IA]; R_f = 0.27 (*n*-pentane/Et_2O, 4:1).

IR (ATR): 3495, 3075, 2922, 2665, 2329, 2087, 1996, 1936, 1752, 1642, 1588, 1556, 1471, 1430, 1376, 1299, 1192, 1070, 998, 946, 874, 816, 769, 675 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.64–7.60 (m, 1 H, CH_{Ar}), 7.42–7.37 (m, 2 H, CH_{Ar}), 7.34 (t, *J* = 8.1 Hz, 2 H, CH_{Ar}), 7.31–7.25 (m, 3 H, CH_{Ar}), 7.18 (dt, *J* = 12.0, 2.1 Hz, 2 H, CH_{Ar}), 7.07 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1 H, CH_{Ar}), 7.05 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1 H, CH_{Ar}), 6.13 (d, *J* = 1.2 Hz, 1 H, CH_{ol}), 5.86 (d, *J* = 1.2 Hz, 1 H, CH_{ol}), 5.10–5.03 (m, 2 H, C*H*HNO_2, C*H*CH_2), 4.95 (dd, *J* = 16.8, 8.6 Hz, 1 H, CH*H*NO_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.6, 166.2, 150.8, 150.4, 143.9, 139.9, 137.8, 135.0, 135.0, 130.5, 130.5, 130.4, 129.2, 127.1, 127.0, 123.9, 121.7, 121.7, 121.6, 119.4, 119.4, 112.1, 76.0, 66.9, 47.8.

MS (EI, 70 eV): *m*/*z* (%) = 450.1 (11), 295.1 (26), 267.2 (18), 231.1 (26), 216.1 (100), 168.1 (27).

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{17}NO_6Cl_2Na^+$: 520.0325; found: 520.0325.

Bis(4-chlorophenyl) (*S*)-1-Methylene-3-(nitromethyl)-1,3-dihydro-2*H*-indene-2,2-dicarboxylate (4n)

Compound **4n** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 146 mg (98%); yellowish oil; $[\alpha]_D^{23}$ –26.0 (*c* 0.2, $CHCl_3$); 86% *ee* [HPLC: Chiralcel OD]; R_f = 0.32 (*n*-pentane/Et_2O, 4:1).

IR (ATR): 3886, 3473, 3068, 2672, 2330, 2090, 1891, 1746, 1559, 1480, 1194, 1088, 820 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.63–7.59 (m, 1 H, CH_{Ar}), 7.41–7.35 (m, 6 H, CH_{Ar}), 7.30–7.27 (m, 1 H, CH_{Ar}), 7.12–7.06 (m, 4 H, CH_{Ar}), 6.12 (d, *J* = 1.0 Hz, 1 H, CH_{ol}), 5.85 (d, *J* = 0.8 Hz, 1 H, CH_{ol}), 5.08–5.03 (m, 2 H, C*H*HNO_2, C*H*CH_2), 4.94 (dd, *J* = 16.6, 8.2 Hz, 1 H, CH*H*NO_2).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 166.9, 166.5, 148.9, 148.5, 144.0, 139.9, 137.9, 132.2, 132.1, 130.3, 129.8 (2 C), 129.8 (2 C), 129.2, 123.9, 122.4 (2 C), 122.4 (2 C), 121.6, 112.0, 75.9, 66.9, 47.8.

MS (EI, 70 eV): *m*/*z* (%) = 450.6 (3), 370.6 (10), 295.5 (25), 216.5 (62), 168.4 (100), 155.4 (34), 141.4 (71), 128.2 (48).

HRMS (ESI): *m*/*z* $[M - HNO_2]^+$ calcd for $C_{25}H_{16}O_4Cl_2^+$: 450.0420; found: 450.0422.

(*R*)-1-(3-Methyl-1-(nitromethyl)-1*H*-inden-2-yl)ethan-1-one (5a)

Compound **5a** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 16 mg (23%); colorless solid; mp 83–84 °C; $[\alpha]_D^{23}$ –123.3 (*c* 0.4, $CHCl_3$); 98% *ee* [HPLC: Chiralpak IC]; R_f = 0.21 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3438, 2924, 2337, 2092, 1921, 1710, 1639, 1545, 1430, 1358, 1245, 1163, 1002, 925, 843, 757 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.57–7.51 (m, 1 H, CH_{Ar}), 7.43 (dt, *J* = 7.7, 4.1 Hz, 1 H, CH_{Ar}), 7.40 (d, *J* = 4.0 Hz, 2 H, CH_{Ar}), 5.18 (dd, *J* = 12.3, 4.0 Hz, 1 H, C*H*HNO_2), 4.51 (dd, *J* = 12.3, 8.1 Hz, 1 H, CH*H*NO_2), 4.47–4.40 (m, 1 H, C*H*CH_2), 2.57 (s, 3 H, $COCH_3$), 2.55 (d, *J* = 2.1 Hz, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.9, 150.7, 144.4, 143.3, 138.9, 129.3, 128.4, 123.5, 122.3, 76.1, 47.4, 31.2, 13.7.

MS (EI, 70 eV): *m*/*z* (%) = 232.3 (31) $[M + H]^+$, 185.3 (35), 169.2 (86), 159.2 (100), 141.2 (70), 115.2 (65).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{13}NO_3^+$: 231.0890; found: 231.0898.

(*R*)-1-(6-Chloro-3-methyl-1-(nitromethyl)-1*H*-inden-2-yl)ethan-1-one (5b)

Compound **5b** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 27 mg (34%); colorless solid; mp 122–124 °C; $[\alpha]_D^{23}$ –48.8 (*c* 0.3, $CHCl_3$); 98% *ee* [HPLC: Chiralpak IC]; R_f = 0.25 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3263, 2928, 2315, 2096, 1912, 1740, 1628, 1550, 1353, 1252, 1159, 1070, 984, 832 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.49–7.44 (m, 1 H, CH_{Ar}), 7.43–7.38 (m, 2 H, CH_{Ar}), 5.15 (dd, *J* = 12.7, 3.9 Hz, 1 H, C*H*HNO_2), 4.55 (dd, *J* = 12.7, 7.9 Hz, 1 H, CH*H*NO_2), 4.42 (ddd, *J* = 7.8, 3.9, 2.0 Hz, 1 H, C*H*CH_2), 2.57 (s, 3 H, $COCH_3$), 2.53 (d, *J* = 2.1 Hz, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.6, 149.6, 144.9, 143.0, 139.0, 135.6, 128.9, 124.1, 123.3, 75.6, 47.2, 31.1, 13.7.

MS (EI, 70 eV): *m*/*z* (%) = 266.0 (39) $[M + H]^+$, 218.0 (76), 203.0 (100).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}NO_3Cl^+$: 265.0500; found: 265.0501.

(*R*)-1-(6-Fluoro-3-methyl-1-(nitromethyl)-1*H*-inden-2-yl)ethan-1-one (5c)

Compound **5c** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 40 mg (54%); colorless solid; mp 130–132 °C; $[\alpha]_D^{23}$ –163.9 (*c* 0.7, $CHCl_3$); 98% *ee* [HPLC: Chiralpak IC]; R_f = 0.21 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3456, 3245, 3060, 2661, 2329, 2093, 1912, 1741, 1612, 1539, 1429, 1354, 1270, 1197, 1099, 841, 668 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55–7.42 (m, 1 H, CH_{Ar}), 7.19–7.07 (m, 2 H, CH_{Ar}), 5.17 (dd, *J* = 12.6, 4.0 Hz, 1 H, C*H*HNO_2), 4.51 (dd, *J* = 12.6, 8.1 Hz, 1 H, CH*H*NO_2), 4.44–4.40 (m, 1 H, C*H*CH_2), 2.56 (s, 3 H, $COCH_3$), 2.53 (d, *J* = 2.1 Hz, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.4, 163.8 (d), 149.9, 145.7 (d), 140.4 (d), 138.7 (d), 123.7 (d), 115.8 (d), 111.5 (d), 75.8, 47.2 (d), 31.0, 13.8.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –110.23 (td, *J* = 8.6, 5.1 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 249.9 (97) $[M + H]^+$, 202.9 (76), 186.9 (100).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}NO_3F^+$: 249.0796; found: 249.0805.

(*R*)-1-(6-Methoxy-3-methyl-1-(nitromethyl)-1*H*-inden-2-yl)ethan-1-one (5d)

Compound **5d** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 78 mg (99%); colorless solid; mp 107–109 °C; $[\alpha]_D^{23}$ –118.6 (*c* 0.5, $CHCl_3$); ≥99% *ee* [HPLC: Chiralpak IA]; R_f = 0.21 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3413, 3088, 2921, 2846, 2606, 2291, 2113, 1998, 1894, 1706, 1620, 1574, 1475, 1421, 1368, 1343, 1278, 1225, 1178, 1137, 1089, 1026, 948, 877, 827, 772, 723, 661 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4 Hz, 1 H, CH_{Ar}), 6.96 (dd, *J* = 8.5, 2.3 Hz, 1 H, CH_{Ar}), 6.92 (d, *J* = 2.2 Hz, 1 H, CH_{Ar}), 5.19 (dd, *J* = 11.0, 2.5 Hz, 1 H, C*H*HNO_2), 4.48–4.35 (m, 2 H, CH*H*NO_2, C*H*CH_2), 3.83 (s, 3 H, OCH_3), 2.54 (s, 3 H, $COCH_3$), 2.52 (d, *J* = 1.7 Hz, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.2, 161.4, 151.2, 145.9, 137.2, 137.0, 123.4, 114.7, 109.2, 76.3, 55.6, 47.1, 30.9, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 260.9 (71) $[M]^+$, 213.9 (83), 199.0 (100).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}NO_4^+$: 262.1074; found: 262.1072.

(*R*)-1-(7-Methyl-5-(nitromethyl)-5*H*-indeno[5,6-*d*][1,3]dioxol-6-yl)ethan-1-one (5e)

Compound **5e** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 57 mg (69%); colorless solid; mp 102–104 °C; $[\alpha]_D^{23}$ –126.8 (*c* 0.4, $CHCl_3$); 95% *ee* [HPLC: Chiralpak IB]; R_f = 0.30 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3448, 3251, 2916, 2783, 2698, 2326, 2105, 1996, 1864, 1705, 1633, 1537, 1472, 1434, 1372, 1330, 1216, 1157, 1110, 1028, 930, 871, 834, 739, 665 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.96 (s, 1 H, CH_{Ar}), 6.87 (s, 1 H, CH_{Ar}), 6.03 (dd, *J* = 6.1, 1.3 Hz, 2 H, OCH_2O), 5.15 (dd, *J* = 12.4, 4.0 Hz, 1 H, C*H*HNO_2), 4.44 (dd, *J* = 12.4, 8.2 Hz, 1 H, CH*H*NO_2), 4.33 (ddd, *J* = 8.0, 3.7, 1.9 Hz, 1 H, C*H*CH_2), 2.53 (s, 3 H, $COCH_3$), 2.48 (d, *J* = 2.0 Hz, 3 H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 194.8, 150.9, 149.6, 148.5, 138.8, 138.5, 138.0, 104.6, 102.5, 101.8, 76.3, 47.0, 30.9, 14.0.

MS (EI, 70 eV): *m*/*z* (%) = 274.9 (61) $[M]^+$, 228.0 (64), 212.9 (100).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{13}NO_5^+$: 275.0788; found: 275.0793.

(*R*)-1-(3-Methyl-1-(nitromethyl)-1*H*-inden-2-yl)propan-1-one (5f)

Compound **5f** was isolated after flash chromatography (*n*-pentane/Et_2O, 3:1); yield: 44 mg (60%); colorless solid; mp 87–89 °C; $[\alpha]_D^{23}$ –97.5 (*c* 0.2, $CHCl_3$); 97% *ee* [HPLC: Chiralpak AS]; R_f = 0.59 (*n*-pentane/Et_2O, 1:1).

IR (ATR): 3817, 3390, 2927, 2676, 2336, 2094, 1877, 1755, 1629, 1550, 1361, 1199, 1035, 919, 758 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.46–7.37 (m, 3 H, CH_{Ar}), 5.17 (dd, *J* = 12.1, 3.8 Hz, 1 H, C*H*HNO_2), 4.51 (dd, *J* = 12.1, 8.0 Hz, 1 H, CH*H*NO_2), 4.48–4.43 (m, 1 H, C*H*CH_2), 2.89 (tdd, *J* = 17.3, 10.1, 7.2 Hz, 2 H, C*H*$_2$$CH_3$), 2.54 (d, *J* = 2.0 Hz, 3 H, =CCH_3), 1.21 (t, *J* = 7.2 Hz, 3 H, CH_2C*H*$_3$).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 199.1, 149.6, 144.5, 143.3, 138.6, 129.1, 128.4, 123.4, 122.2, 76.2, 47.5, 36.3, 13.8, 8.1.

MS (EI, 70 eV): *m*/*z* (%) = 245.5 (2) $[M]^+$, 216.4 (2), 199.4 (4), 173.3 (7), 169.3 (35), 141.3 (17), 57.3 (100).

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{15}NO_3^+$: 245.1052; found: 245.1057.

Acknowledgment

We thank the European Research Council (ERC Advanced Grant 320493 'DOMINOCAT') for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588113.

References

(1) (a) Vilums, M.; Heuberger, J.; Heitman, L. H.; Ijzerman, A. P. *Med. Res. Rev.* **2015**, *35*, 1097. (b) Gabriele, B.; Mancuso, R.; Veltri, L. *Chem. Eur. J.* **2016**, *22*, 5056.

(2) For selected indane examples, see: (a) Daum, S.; Erdmann, F.; Fischer, G.; Féaux de Lacroix, B.; Hessamian-Alinejad, A.; Houben, S.; Frank, W.; Braun, M. *Angew. Chem. Int. Ed.* **2006**, *45*, 7454. (b) Gross, M. F.; Beaudoin, S.; McNaughton-Smith, G.; Amato, G. S.; Castle, N. A.; Huang, C.; Zou, A.; Yu, W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2849. (c) Sharma, M.; Ray, S. M. *Eur. J. Med. Chem.* **2008**, *43*, 2092. (d) Shiohara, H.; Nakamura, T.; Kikuchi, N.; Ozawa, T.; Nagano, R.; Matsuzawa, A.; Ohnota, H.; Miyamoto, T.; Ichikawa, K.; Hashizume, K. *Bioorg. Med. Chem.* **2012**, *20*, 3622. (e) Ugliarolo, E. A.; Gagey, D.; Lantaño, B.; Moltrasio, G. Y.; Campos, R. H.; Cavallaro, L. V.; Moglioni, A. G. *Bioorg. Med. Chem.* **2012**, *20*, 5986. (f) Kumar, S.; Dwivedi, A. P.; Kashyap, V. K.; Saxena, A. K.; Dwivedi, A. K.; Srivastava, R.; Sahu, D. P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2404. (g) Dutt, R.; Madan, A. K. *Med. Chem. Res.* **2013**, *22*, 3213. (h) Singh, A.; Fatima, K.; Singh, A.; Behl, A.; Mintoo, M. J.; Hasanain, M.; Ashraf, R.; Luqman, S.; Shanker, K.; Mondhe, D. M.; Sarkar, J.; Chanda, D.; Negi, A. S. *Eur. J. Pharm. Sci.* **2015**, *76*, 57.

(3) For selected indene examples, see: (a) Voets, M.; Antes, I.; Scherer, C.; Müller-Vieira, U.; Biemel, K.; Marchais-Oberwinkler, S.; Hartmann, R. W. *J. Med. Chem.* **2006**, *49*, 2222. (b) Ahn, J. H.; Shin, M. S.; Jung, S. H.; Kim, J. A.; Kim, H. M.; Kim, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Park, S. D.; Lee, J. M.; Lee, J. H.; Cheon, H. G.; Kim, S. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5239. (c) Tu, S.; Xu, L.-H.; Ye, L.-Y.; Wang, X.; Sha, Y.; Xiao, Z.-Y. *J. Agric. Food Chem.* **2008**, *56*, 5247. (d) Norrgård, M. A.; Mannervik, B. *J. Mol. Biol.* **2011**, *412*, 111. (e) Kahlon, A. K.; Negi, A. S.; Kumari, R.; Srivastava, K. K.; Kumar, S.; Darokar, M. P.; Sharma, A. *Appl. Microbiol. Biotechnol.* **2014**, *98*, 2041. (f) Banothu, J.; Basavoju, S.; Bavantula, R. *J. Heterocycl. Chem.* **2015**, *52*, 853.

(4) Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I. W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443.

(5) Villetti, G.; Bregola, G.; Bassani, F.; Bergamaschi, M.; Rondelli, I.; Pietra, C.; Simonato, M. *Neuropharmacology* **2001**, *40*, 866.

(6) Jung, M.; Wahl, A. F.; Neupert, W.; Geisslinger, G.; Senter, P. D. *Pharm. Pharmacol. Commun.* **2000**, *6*, 217.

(7) Yu, H.; Kim, I. J.; Folk, J. E.; Tian, X.; Rothman, R. B.; Baumann, M. H.; Dersch, C. M.; Flippen-Anderson, J. L.; Parrish, D.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2004**, *47*, 2624.

(8) Juby, P. F.; Partyka, R. A.; Hudyma, T. W. US Patent 3565943, **1971**.

(9) (a) Sun, S.-S.; Zhang, C.; Yang, Z.; Dalton, L. R.; Garner, S. M.; Chen, A.; Steier, W. H. *Polymer* **1998**, *39*, 4977. (b) Yang, J.; Lakshmikantham, M. V.; Cava, M. P.; Lorcy, D.; Bethelot, J. R. *J. Org. Chem.* **2000**, *65*, 6739. (c) Diesendruck, C. E.; Steinberg, B. D.; Sugai, N.; Silberstein, M. N.; Sottos, N. R.; White, S. R.; Braun, P. V.; Moore, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 12446. (d) Morales, A. R.; Frazer, A.; Woodward, A. W.; Ahn-White, H.-Y.; Fonari, A.; Tongwa, P.; Timofeeva, T.; Belfield, K. D. *J. Org. Chem.* **2013**, *78*, 1014.

(10) (a) Barberá, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem. Int. Ed.* **1998**, *37*, 296. (b) Konstantinova, L. S.; Rakitin, O. A.; Souvorova, L. I.; Rees, C. W.; White, A. J. P.; Williams, D. J.; Torroba, T. *Chem. Commun.* **1999**, 73. (c) Basurto, S.; García, S.; Neo, A. G.; Torroba, T.; Marcos, C. F.; Miguel, D.; Barberá, J.; Ros, M. B.; de la Fuente, M. R. *Chem. Eur. J.* **2005**, *11*, 5362. (d) Mohammady, S. Z.; Elkholy, S. S.; Elsabee, M. Z. *Polym. Int.* **2007**, *56*, 7. (e) He, Y.; Zhao, G.; Peng, B.; Li, Y. *Adv. Funct. Mater.* **2010**, *20*, 3383. (f) Xia, Z.-Y.; Zhang, Z.-Y.; Su, J.-H.; Zhang, Q.; Fung, K.-M.; Lam, M.-K.; Li, K.-F.; Wong, W.-Y.; Cheah, K.-W.; Tian, H.; Chen, C. H. *J. Mater. Chem.* **2010**, *20*, 3768. (g) He, Y.; Chen, H.-Y.; Hou, J.; Li, Y. *J. Am. Chem. Soc.* **2010**, *132*, 1377. (h) He, Y.; Li, Y. *Phys. Chem. Chem. Phys.* **2011**, *13*, 1970. (i) Seyler, H.; Wong, W. W. H.; Jones, D. J.; Holmes, A. B. *J. Org. Chem.* **2011**, *76*, 3551. (j) Matano, Y.; Saito, A.; Suzuki, Y.; Miyajima, T.; Akiyama, S.; Otsubo, S.; Nakamoto, E.; Aramaki, S.; Imahori, H. *Chem. Asian J.* **2012**, *7*, 2305. (k) Barrera, E. G.; Stedile, F. C.; de Souza, M. O.; Miranda, M. S. L.; de Souza, R. F.; Bernardo-Gusmão, K. *Appl. Catal., A* **2013**, *462-463*, 1.

(11) (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Du, Z.; Shao, Z. *Chem. Soc. Rev.* **2013**, *42*, 1337.

(12) Loh, C. C. J.; Badorrek, J.; Raabe, G.; Enders, D. *Chem. Eur. J.* **2011**, *17*, 13409.

(13) Hack, D.; Dürr, A. B.; Deckers, K.; Chauhan, P.; Seling, N.; Rübenach, L.; Mertens, L.; Raabe, G.; Schoenebeck, F.; Enders, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 1797.

(14) (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. (b) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366. (c) Hack, D.; Blümel, M.; Chauhan, P.; Philipps, A. R.; Enders, D. *Chem. Soc. Rev.* **2015**, *44*, 6059.

(15) (a) Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025. (b) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140. (c) Ramachary, D. B.; Mondal, R.; Venkaiah, C. *Eur. J. Org. Chem.* **2010**, 3205. (d) Montaignac, B.; Vitale, M. R.; Ratovelomanana-Vidal, V.; Michelet, V. *J. Org. Chem.* **2010**, *75*, 8322. (e) Montaignac, B.; Vitale, M. R.; Michelet, V.; Ratovelomanana-Vidal, V. *Org. Lett.* **2010**, *12*, 2582. (f) Praveen, C.; Montaignac, B.; Vitale, M. R.; Ratovelomanana-Vidal, V.; Michelet, V. *ChemCatChem* **2013**, *5*, 2395.

(16) (a) Capdevila, M. G.; Benfatti, F.; Zoli, L.; Stenta, M.; Cozzi, P. G. *Chem. Eur. J.* **2010**, *16*, 11237. (b) Motoyama, K.; Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Eur. J. Org. Chem.* **2011**, 2239. (c) Sinisi, R.; Vita, M. V.; Gualandi, A.; Emer, E.; Cozzi, P. G. *Chem. Eur. J.* **2011**, *17*, 7404. (d) Guiteras Capdevila, M.; Emer, E.; Benfatti, F.; Gualandi, A.; Wilson, C. M.; Cozzi, P. G. *Asian J. Org. Chem.* **2012**, *1*, 38. (e) Xiao, J. *Org. Lett.* **2012**, *14*, 1716. (f) Gualandi, A.; Mengozzi, L.; Wilson, C. M.; Cozzi, P. G. *Synthesis* **2014**, *46*, 1321.

(17) (a) Kim, S.-G.; Park, T.-H.; Kim, B. J. *Tetrahedron Lett.* **2006**, *47*, 6369. (b) Lim, A.; Choi, J. H.; Tae, J. *Tetrahedron Lett.* **2008**, *49*, 4882.

(18) Lv, J.; Zhang, L.; Zhou, Y.; Nie, Z.; Luo, S.; Cheng, J.-P. *Angew. Chem. Int. Ed.* **2011**, *50*, 6610.

(19) Lv, J.; Zhang, L.; Hu, S.; Cheng, J.-P.; Luo, S. *Chem. Eur. J.* **2012**, *18*, 799.

(20) For recent indane syntheses undertaken by our group, see: (a) Loh, C. C. J.; Hack, D.; Enders, D. *Chem. Commun.* **2013**, *49*, 10230. (b) Loh, C. C. J.; Atodiresei, I.; Enders, D. *Chem. Eur. J.* **2013**, *19*, 10822. (c) Loh, C. C. J.; Chauhan, P.; Hack, D.; Lehmann, C.; Enders, D. *Adv. Synth. Catal.* **2014**, *356*, 3181.

(21) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

(22) (a) Nakamura, M.; Liang, C.; Nakamura, E. *Org. Lett.* **2004**, *6*, 2015. (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (c) Itoh, Y.; Tsuji, H.; Yamagata, K.-i.; Endo, K.; Tanaka, I.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161. (d) Montel, S.; Bouyssi, D.; Balme, G. *Adv. Synth. Catal.* **2010**, *352*, 2315. (e) Chan, L. Y.; Kim, S.; Park, Y.; Lee, P. H. *J. Org. Chem.* **2012**, *77*, 5239. (f) Boominathan, S. S. K.; Hu, W.-P.; Senadi, G. C.; Wang, J.-J. *Adv. Synth. Catal.* **2013**, *355*, 3570.

(23) Kochetkov, N. K.; Kudryashov, L. J.; Gottich, B. P. *Tetrahedron* **1961**, *12*, 63.

(24) Mander, L. N.; Woolias, M. *Synthesis* **1979**, 185.

(25) Jabin, I.; Revial, G.; Monnier-Benoit, N.; Netchitaïlo, P. *J. Org. Chem.* **2001**, *66*, 256.