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Stereoselective Synthesis of Functionalized Chiral 2-Nitrocyclohexanecarboxylic Esters *via* Catalytic Dienamine Addition to β-Substituted β-Nitroacrylates

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Abstract: A metal-free stereoselective catalytic addition of *in situ* generated dienamine to β-nitroacrylates has been developed. Starting from simple α,β-unsaturated ketones, highly functionalized chiral β-nitrocyclohexanecarboxylic esters were obtained in a single step, in good yields and up to 98% *ee*. By an unprecedented mechanistic pathway, starting from the synthetically readily available *E*-nitroacrylate, the present methodology allowed us to obtain as major product the isomer bearing a *cis* relative disposition between the nitro and the ester groups, which is not accessible *via* a classical Diels–Alder reaction.

Keywords: bifunctional catalysts; cyclohexanecarboxylic esters; dienamines; nitroacrylates; organocatalysis

Introduction

Chiral β-amino acids are a subject of extraordinary interest because of their presence in many natural products,[1] biologically active compounds,[2] and their use as starting materials for the preparation of β-lactam antibiotics.[3] Recently they have gained new attention as constituents of β-peptides, unnatural oligomers characterized by a high resistance to peptide-catalyzed hydrolysis.[4] Interestingly, it was observed that peptides containing cyclic amino acids tend to adopt a more regular secondary structure than those based on acyclic residues.[5] Moreover, β-amino esters carrying a hydroxy function have proved to be difficult to obtain, and this is unfortunate in light of the considerable importance of these molecules, present in many important products, like taxol, bestatin and related compounds.[6] Additionally, nitrocyclohexanones have been recognized as important and flexible precursors for the synthesis of some alkaloid derivatives in the lycorine, crinine and caranine series (Figure 1).[7]

The cycloaddition between nitroacrylates and properly functionalized dienes may be envisaged as a viable synthetic approach for the stereoselective synthesis of chiral β-aminocyclohexanecarboxylic acids; indeed, Barluenga has already explored that strategy by studying the reaction between an aminodiene and nitroalkenes, employing a chiral auxiliary at the diene residue to control the absolute stereochemistry of the process.[8]

In the attempt to develop a catalytic methodology for the synthesis of functionalized cyclohexanecarboxylic acids, we have thought to take advantage of the recent progress in the field of organocatalysis,[9] where impressive results have been obtained in the activation of unsaturated ketones *via* amino catalysis.[10] Recently Melchiorre and List have reported that *Cinchona*-based primary amines can be exploited to activate α,β-unsaturated ketones and enals,[11] and reacted them *via* dienamine catalysis with different electrophilic partners, including nitroalkenes.

However, although many reports in organocatalysis have focused on the electrophilic reactivity of nitroalkenes (especially nitrostyrene derivatives),[12] much less is known on the use of nitroacrylates.[13] A few years ago, in a study by Seidel on the addition of in-

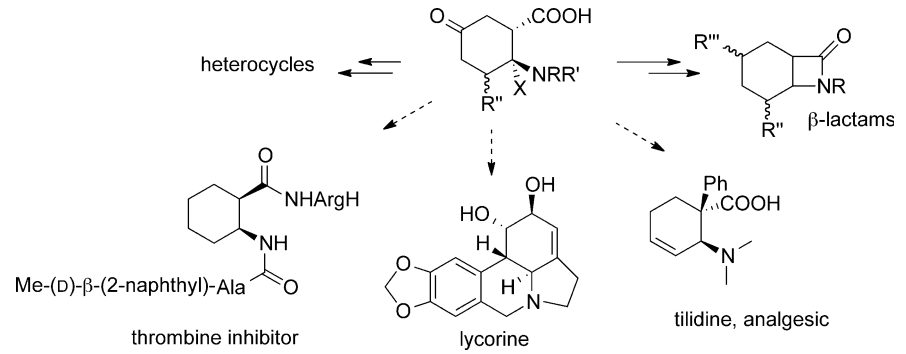
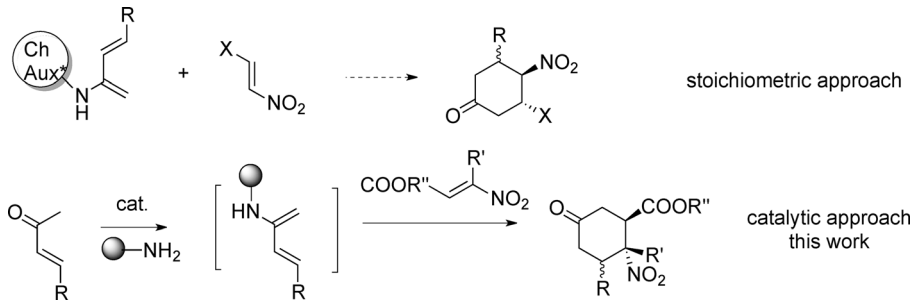


Figure 1. Some representative aminocyclohexanecarboxylic acid derivatives of biological interest.



Scheme 1. Organocatalytic approach to the synthesis of highly functionalized cyclohexanecarboxylic acids.

doles to nitroalkenes catalyzed by quinolium thioamides, a single example of the reaction of 3-nitroacrylate was described.[14] In 2008 List reported the enantioselective reduction *via* transfer hydrogenation of β-nitroacrylates.[15] In 2010 the organocatalytic conjugate addition of oximes to β-nitroacrylates has been developed.[16] More recently, Wennemers successfully accomplished a highly stereoselective addition of aldehydes to α-substituted β-nitroacrylates;[17] the tripeptide-catalyzed transformation generated all-carbon quaternary stereocenters, thus showing the great potential of the methodology (Scheme 1).[18]

However, the catalytic direct addition of unsaturated ketones to nitroacrylates is largely underdeveloped;[19] therefore we decided to investigate in detail the organocatalyzed reaction of nitroacrylates with *in situ* generated dienamine.[20]

Results and Discussion

β-Alkyl-substituted β-nitroacrylates were easily prepared[21] and used in reactions promoted by bifunctional organocatalysts. After a preliminary investigation,[22] our attention focused on the use of *Cinchona* derivatives (Figure 2).[23] The reaction between 4-phenyl-2-butanone **1** and ethyl (*E*)-3-ethyl-3-nitroacrylate **2** was selected as a model transformation.

The reaction was typically performed in toluene at 40 °C by mixing two mol equiv. of ketone and one mol equiv. of nitroacrylate, in the presence of a 20 mol% amount of the catalyst and 30 mol% of salicylic acid (Table 1).

As expected on the basis of previous studies, the addition of a catalytic amount of an acidic additive

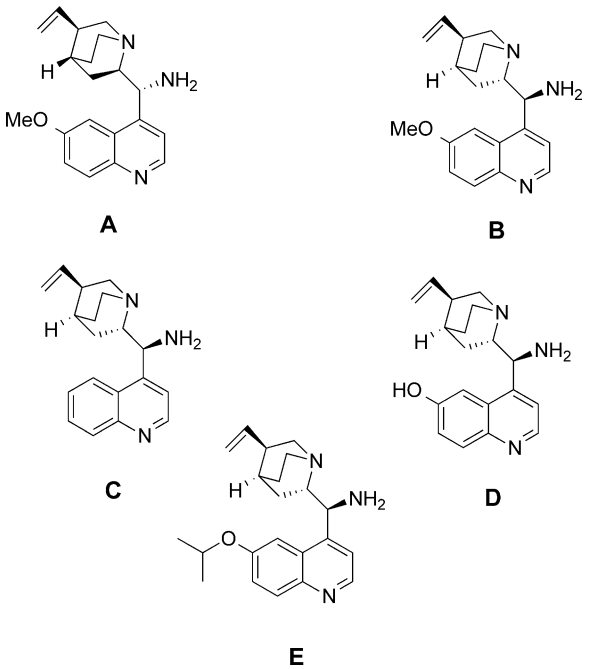


Figure 2. A few selected chiral organocatalysts employed in the present study.

Table 1. Preliminary studies with organocatalysts **A–E**.

Entry	Cat.	Time [h]	Yield [%][a]	**3a/3b**[b]	*ee* [%][c]
1[d]	**A**	48	n.r.	–	–
2	**A**	48	55	33/67	(+) 92/87
3	**B**	48	57	13/87	(−) 90/93
4	**A**	24	83	30/70	(+) 89/85
5	**B**	24	75	20/80	(−) 97/95
6	**C**	24	45	30/70	(−) 95/92
7[e]	**D**	24	71	50/50	(−) 83/90
8	**E**	24	87	30/70	(−) 92/96
9[f]	**A**	48	57	15/85	(+) 90/93

[a] Reaction run in toluene at 40 °C; isolated yields after chromatography.
[b] Diastereoisomeric ratio determined by NMR on the crude reaction mixture and confirmed after purification.
[c] Enantiomeric excess determined by HPLC on a chiral stationary phase (see the Supporting Information for details), use of cat. **B–E** led to the major enantiomers of **3a** and **3b** with opposite configuration to those obtained with cat. **A**.
[d] Reaction performed without salicylic acid.
[e] Reaction performed in CH_2Cl_2.
[f] Reaction performed starting from ethyl (*Z*)-3-ethyl-3-nitroacrylate.

Table 2. Optimization studies with catalyst **A**.

Entry	Solvent	Temp. [°C]	Yield [%][a]	**3a/3b**[b]	*ee* [%][c]
1	toluene	40	55	33/67	(+) 92/87
2	toluene	60	57	48/52	(+) 94/81
3	toluene	25	72	33/67	(+) 96/93
4	toluene	5	61	20/80	(+) 93/92
5[d]	toluene	40	57	33/67	(+) 95/90
6[e]	toluene	40	80	50/50	(+) 70/75
7	DCM	40	80	25/75	(+) 87/83
8	EtOH	40	70	30/70	(+) 91/70
9	DMSO	40	41	50/50	(+) 77/76
10	water	40	37	15/85	(+) 91/87
11[f]	toluene	40	40	50/50	(+) 95/70
12[g]	toluene	40	61	47/53	(+) 93/78
13[h]	toluene	40	50	48/52	(+) 83/72

[a] Reaction time: 48 h; isolated yields after chromatographic purification.
[b] Diastereoisomeric ratio determined by NMR on the crude reaction mixture and confirmed after purification.
[c] Enantiomeric excess determined by HPLC on chiral stationary phase (see the Supporting Information for details.
[d] Ketone/acrylate ratio 1/1.
[e] Ketone/acrylate 1/2.
[f] Additive: acetic acid.
[g] Additive: 2-F-benzoic acid.
[h] Additive: 4-OH-benzoic acid.

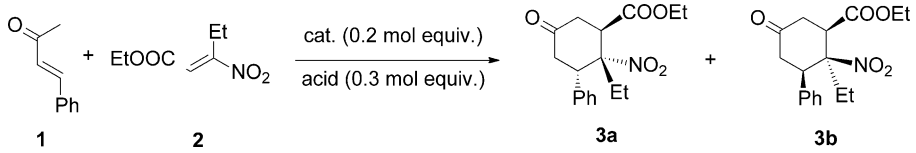
was found to be essential to promote the transformation.[24] 9-Amino(9-deoxy)-*epi*-quinidine **A**, in the presence of salicylic acid, was indeed able to activate ketone **1** *via* dienamine, that reacted with (*E*)-nitroacrylate **2** to afford the 2-nitro-3-phenyl-5-ketocyclohexanecarboxylic ethyl ester **3** as mixture of two diastereoisomers; noteworthy both isomers were obtained with very high enantioselectivities (92% and 87% *ee*, respectively, entries 1 and 2 of Table 1).

When the *quasi*-enantiomeric quinine derivative **B** was used, virtually identical *ee* values (but for the opposite absolute configuration) for both stereoisomers were observed, leading to the products **3a** and **3b** shown in Scheme 2, with an increased diastereoselectivity (entry 3, Table 1). Very good results were obtained also for shorter reaction times, when enantioselectivities up to 97% were reached. A preliminary survey of catalyst structural variations showed that neither the presence of an OH group possibly engaged in hydrogen bond-based recognition phenomena, nor the modification of the OR substituent at the quinoline ring influenced the catalyst behaviour.

Interestingly, when the (*Z*) isomer of acrylate **2** was employed, the same reaction products were isolated, with the same level of enantioselectivity (90% and 93%), and a slightly increased diastereoselectivity (**3a/3b** 15/85, entry 9, Table 1).

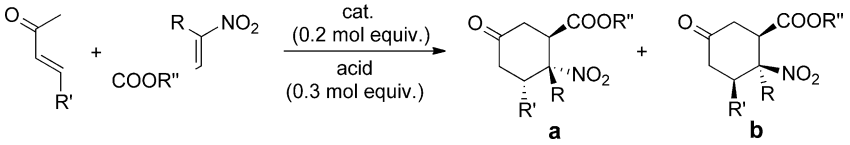
In looking for the best experimental conditions, several parameters were investigated; a few, selected results of the optimization studies are shown in Table 2. Reaction temperature did not show any appreciable influence on yield and stereoselectivity; however generally by operating at 25 °C the highest *ee* were observed.

Toluene seems to be the best solvent, but also chlorinated solvents may be used without compromising significantly the stereoselectivity. A drop in the enantioselection was registered by running the reaction in DMSO, while in pure water interesting levels of *ee* were recorded, although in low yields. Noteworthy the acidic additive seems not to have a decisive role in determining the stereochemical outcome of



Scheme 2. Model reaction between 4-phenyl-2-butanone **1** and ethyl 3-ethyl-3-nitroacrylate **2**.

Table 3. General applicability of the catalytic approach.



Entry	n.	Cat.	Yield [%][a]	R	R′	R″	a/b *dr*[b]	*ee* [%][c]
1	**3**	**B**	57	Et	Ph	Et	13/87	(−) 90/93
2	**en3**	**A**	55	Et	Ph	Et	33/67	(+) 92/87
3	**en4**	**A**	67	Pent	Ph	Et	33/67	(+) 83/86
4	**4**	**B**	70	Pent	Ph	Et	30/70	(−) 96/94
5	**en5**	**A**	57	Et	4-BrC_6H_4	Et	45/55	(+) 93/81
6	**5**	**B**	45	Et	4-BrC_6H_4	Et	47/53	(−) 94/92
7[d]	**5**	**B**	55	Et	4-BrC_6H_4	Et	30/70	(−) 94/98
8	**en6**	**A**	81	Et	2-thienyl	Et	12/88	(+) 91/90
9	**6**	**B**	77	Et	2-thienyl	Et	25/75	(−) 97/98
10	**en7**	**A**	25	Et	Me	Et	25/75	(+) 97/87
11	**7**	**B**	31	Et	Me	Et	47/53	(−) 97/93
12	**en8**	**A**	71	Et	Ph	*i*-Pr	20/80	(+) 90/84
13	**8**	**B**	80	Et	Ph	*i*-Pr	12/88	(−) 88/92
14	**en9**	**A**	67	Et	Ph	Bn	30/70	(+) 91/77
15	**9**	**B**	81	Et	Ph	Bn	32/68	(−) 93/90

[a] *Reaction conditions:* toluene, 48 h, 40 °C; isolated yields after chromatographic purification.
[b] Diastereoisomeric ratio determined by NMR on the crude reaction mixture and confirmed after purification.
[c] Enantiomeric excess determined by HPLC on a chiral stationary phase (see the Supporting Information for details).
[d] Reaction performed with 10 mol% amount of catalyst and 15 mol% amount of salicylic acid.

the reaction, although the use of 4-hydroxybenzoic acid instead of 2-hydroxybenzoic acid caused a decrease in the enantioselectivity for both isomers.

The general applicability of the methodology was then investigated, by employing catalysts **A** and **B** as to direct the reaction towards the formation of the two opposite enantiomers of each stereoisomer (Table 3).

The relative configuration of the products was established by NMR studies, while the absolute configuration was determined by X-ray analysis to be 1*R*,2*S*,3*R* for the major isomer of the 4-Br phenyl derivative **5b** (entry 6, Table 3, see Supporting Information). The experimentally observed formation of the major isomer **3b**, bearing a *cis* disposition of the nitro and the ester groups, seems to confirm a stepwise mechanism, involving a Michael addition followed by ring closure, rather than a concerted 4+2 cycloaddition.[25] The proposed reaction mechanism (Figure 3) involves the ketone activation by the catalyst, to generate the dienamine system, that can react with the nitroacrylate in a Michael addition. The transient α,β-unsaturated iminium species thus formed may be attacked by the *in situ* generated nucleophilic carbanionic species (stabilized by the nitro group) to afford the cyclohexane ring.

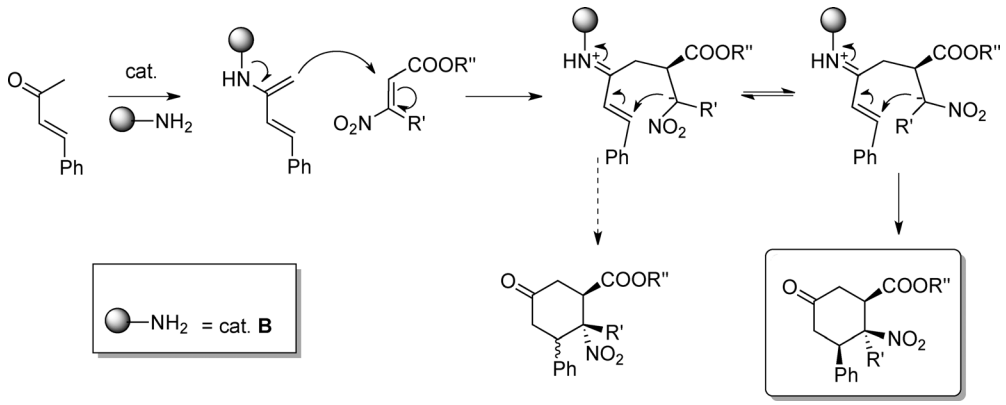
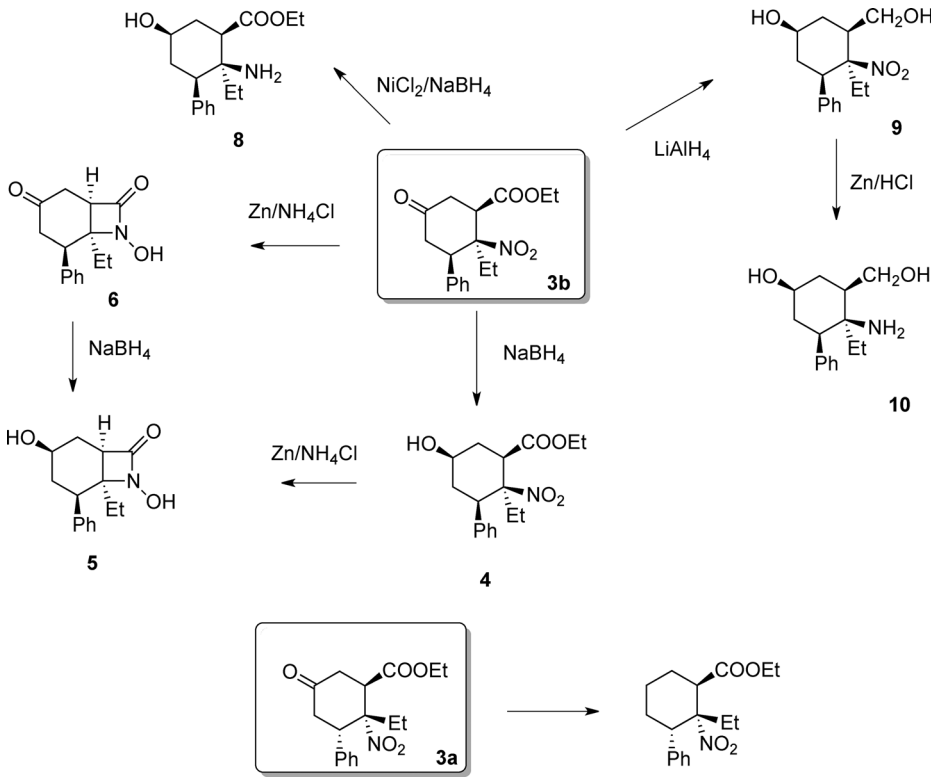


Figure 3. A proposed reaction mechanism.



Scheme 3. Synthetic transformations of chiral 2-nitro-3-aryl-5-ketocyclohexanecarboxylic esters.

Due to the steric hindrance of the α-alkyl-substituted nitro derivative and the stabilization of the carbanionic species, the reaction rate becomes slow enough to allow the equilibrium between the two intermediates **I** and **II** of Figure 3. Stabilizing, electrostatic interactions between the nitro group and the ester moiety may be hypothesized to justify the formation of the never before observed isomer **3b** as the major reaction product.[26]

Finally, the synthetic versatility of the functionalized 2-nitrocyclohexanonecarboxylic ester derivatives was briefly studied (Scheme 3). The enantiomerically pure product **3b** (easily separated by column chromatography) may be selectively reduced at the carbonyl group, to afford the corresponding alcohol **4** as a single isomer. The reduction of the nitro group mediated by Zn afforded the *N*-hydroxy-β-lactam **5.** Noteworthy the same experimental protocol on isomer **3a** led to a different result, affording **7**, the product of a Clemmensen-type reduction of the carbonyl group.[27]

Reduction of both the nitro and the ketone of **3b** could be accomplished with $NiCl_2$ and $NaBH_4$, to afford **8**, while the reaction with $LiAlH_4$ produced the diol **9**, that could be converted to the corresponding dihydroxy amine **11**.

Conclusions

In conclusion, a direct metal-free catalytic stereoselective methodology has been developed to synthesize highly functionalized 2-nitrocyclohexanecarboxylic esters. Molecules bearing one quaternary and two tertiary stereocenters were assembled in a single step, in good yields and up to 98% *ee*.

Experimental Section

General Methods

Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Melting points were determined with a Branstead Electrothermal 9100 capillary melting point apparatus. Flash chromatography was carried out on silica gel (230–400 mesh). Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300) or at 500 MHz (Bruker Advance 500). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ $\delta = 7.26$ ppm). ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier 300 or AMX 300) operating at 75 MHz, or on 500 MHz spectrometers (Bruker Advance 500) operating at 125 MHz, with complete proton decou-

pling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta = 77.0$ ppm). Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Mass spectra (MS) were performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Optical rotations were obtained on a polarimeter at 589 nm using 5 mL or 1 mL cell with a length of 1 dm.

Materials

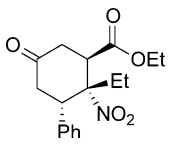
Commercial grade reagents and solvents were used without further purification. Chiral primary amine catalysts **A**–**E** were prepared from commercially available quinine and quinidine, following literature procedures (see the Supporting Information). α,β-Unsaturated ketones were purchased from Aldrich and used as received or synthesized following known procedures. Nitroacrylates were prepared according to literature procedures.[21]

General Procedure for Organocatalytic Reactions

The primary amine catalyst (0.2 equiv.) and the acidic co-catalyst (0.3 equiv.) were dissolved in dry solvent (1 M solution) under an N_2 atmosphere and stirred at room temperature for 10 min. After this period, the α,β-unsaturated ketone and the nitroacrylate were added. The reaction mixture was heated to the desired temperature and stirred for the reported time, after which solvent was removed at reduced pressure. Cyclohexanone derivatives were isolated by flash column chromatography on silica gel. The diastereomeric ratio was determined by ^{1}H NMR analysis on the crude mixture; the enantiomeric ratio was determined by HPLC on chiral stationary phase.

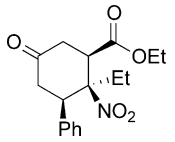
The absolute configuration of the major enantiomer of ethyl 3-(4-bromophenyl)-2-ethyl-2-nitro-5-oxocyclohexanecarboxylate (Table 3, entries 5–6–7, *cis* isomer b) obtained with catalyst **B** (9-deoxy-9-amino-epiquinine) was determined to be 1*R*,2*S*,3*R* by X-ray analysis.

Ethyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (Scheme 2, compound 3a): The product was purified by flash column chromatography on silica gel with a 95:5



hexane/ethyl acetate mixture as eluent. The product appears as an oil. $R_f = 0.25$ (8:2 hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.33$–7.29 (m, 3H), 7.12- 7.06 (m, 2H), 4.33–4.17 (m, 2H), 4.07 (dd, $J = 13.4$, 4.2 Hz, 1H), 3.91 (dd, $J = 7.3$, 3.4 Hz, 1H), 3.36 (dd, $J = 16.8$, 7.3 Hz, 1H), 3.01 (dd, $J = 15.9$, 13.4 Hz, 1H), 2.67–2.57 (m, 2H), 2.12 (hept, $J = 7.5$ Hz, 1H), 1.83 (sex, $J = 7.5$ Hz, 1H), 1.31 (t, 3H, $J = 7.2$ Hz, 3H), 0.95 (t, 3H, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.46 (s), 168.65 (s), 135.63 (s), 128.63 (s), 128.23 (s), 127.31 (s), 90.07 (s), 61.35 (s), 46.22 (s), 45.96 (s), 42.84 (s), 40.02 (s), 25.32 (s), 13.43 (s), 8.63 (s); HR-MS (ESI$^+$): $m/z = 342.13211$ [M+Na], calcd. for $C_{17}H_{21}NO_5Na_1^+$: 342.13119. IR: ν = 3019.98 (Ph), 1729.83 (C=O), 1654.62 (C=O), 1541.81 (NO_2), 1336.43 cm^{-1} (NO_2). The enantiomeric excess was determined by HPLC [Daicel Chiralpack AD column; eluent: 95:5 hexane/*i*-PrOH; flow rate: 0.8 mL min^{-1}; detection: 210 nm]: (+) enantiomer, obtained with catalyst **A**: t_R 13.15 min (minor), t_R 19.35 min (major); (−) enantiomer, obtained with catalyst **B**: t_R 13.52 min (major), t_R 20.32 min (minor); $[\alpha]_D^{23}$: −8° (*ee* 97%, *c* 0.23, $CHCl_3$).

Ethyl 2-ethyl-2-nitro-5-oxo-3-phenylcyclohexanecarboxylate (Scheme 2, compound 3b): The product was purified by flash column chromatography on silica gel with a 95:5



hexane/ethyl acetate mixture as eluent. The product appears as an oil. $R_f = 0.17$ (8:2 hexane/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32$–7.30 (m, 3H), 7.06–7.03 (m, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.36–3.41 (m, 3H), 3.33 (dd, $J = 13.3$, 5.5 Hz, 1H), 2.79 (dd, 1H, $J = 15.2$, 5.3 Hz), 2.57–2.54 (m, 1H), 2.13 (sex, $J = 7.5$ Hz, 1H), 1.87 (sex, $J = 7.5$ Hz, 1H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 205.70$ (s), 171.63 (s), 136.60 (s), 129.16 (s), 128.38 (s), 93.18 (s), 61.94 (s), 47.05 (s), 46.26 (s), 42.61 (s), 40.57 (s), 29.08 (s), 13.98 (s), 7.91 (s); HR-MS (ESI$^+$): $m/z = 342.13099$ [M+Na], calcd. for $C_{17}H_{21}NO_5Na_1^+$: 342.13119. IR: ν = 3019.01 (Ph), 1717.3(C=O), 1653.66 (C=O), 1544.7 cm^{-1} (NO_2). The enantiomeric excess was determined by HPLC [Daicel Chiralpack AD column; eluent: 95:5 hexane/*i*-PrOH; flow rate: 0.8 mL min^{-1}; detection: 210 nm]: (+)-enantiomer, obtained with catalyst **A**: t_R 26.11 min (major), 29.29 min (minor); (−)-enantiomer, obtained with catalyst **B**: t_R 26.01 min (minor), 28.83 min (major). $[\alpha]_D^{23}$: −20.5° (*ee* 88%, *c*: 0.38, $CHCl_3$).

Supporting Information

Experimental details for the catalytic experiments and the synthetic modifications. Analysis and characterization of the reaction products, NMR and HPLC traces of the products, Plot of the X-ray structure of the 4-Br phenyl derivative, crystallographic information file (CIF) and checkCIF report are available in the Supporting Information.

Acknowledgements

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[25] The product with a *cis* relative disposition between the nitro and the ester groups in the cyclohexane ring has never been observed in previous works with nitroalkenes, see refs.[11,16]

[26] Noteworthy, starting from the synthetically available *E*-nitroacrylate, the present methodology allows us to obtain as major product the *cis*-isomer, that is not accessible *via* a classical Diels–Alder reaction.

[27] The different behavior of isomers **3a** and **3b** is a further demonstration of the assigned relative configuration. The unexpected product **7** obtained in the reduction of isomer **3a** is probably due to the great difficulty in reducing the scarcely accessible nitro group. Indeed hydrogenation reactions under different experimental conditions or the use of other reducing agents did not afford the corresponding amines (unreacted starting material was recovered).

