Received: 20 March 2019 | Revised: 9 April 2019 | Accepted: 17 April 2019

DOI: 10.1002/chir.23077

WILEY

REGULAR ARTICLE

Direct enantioselective vinylogous Mannich-type reactions of acyclic enals: New experimental insights into the *E/Z*-dilemma

Michela Vargiu[1] | Lucilla Favero[1] | Andrea Menichetti[1] | Valeria Di Bussolo[2] | Fabio Marchetti[2] | Gennaro Pescitelli[2] | Sebastiano Di Pietro[1] | Mauro Pineschi[1]

[1]Dipartimento di Farmacia, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Pisa, Italy

[2]Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa, Italy

Correspondence
Mauro Pineschi, Dipartimento di Farmacia, Sede di Chimica Bioorganica e Biofarmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa, Italy.
Email: pineschi@farm.unipi.it

Funding information
Università di Pisa, Grant/Award Number: P.R.A. 2016_27

Abstract

The direct heterofunctionalization of acyclic α,β-unsaturated aldehydes with N-acylquinolinium ions contemplating the formation of two stereocentres is studied using dienamine catalysis. This work gives some new experimental insights on the remote stereocontrol in dienamine catalysis using unbiased aliphatic systems and large electrophiles, pointing to a (*Z*)-preference of the reactive configuration of the second double bond.

KEYWORDS

acyclic enals, dienamine catalysis, Mannich reactions, N,O-acetals, vinylogous reactivity

1 | INTRODUCTION

Remote-stereocontrol still represents a challenging task in the field of asymmetric catalysis.[1] Despite the consolidated use of preformed vinylogous nucleophiles in the reaction with classical electrophiles such as carbonyl groups and Michael acceptors,[2] considerably less attention has been devoted to the exploitation of nucleophilic γ-reactivity using unmodified carbonyl compounds. In particular, the γ-nucleophilic character of dienamines derived from α,β-unsaturated aldehydes has been reported for Michael reactions,[3,4] aldol-type reactions,[5,6] S_N1-type alkylation,[7-10] or in cocatalyzed allylation.[11] As regards nitrogen-based electrophiles, besides the seminal paper by Jørgensen in which the γ-amination results from a [4 + 2] cycloaddition process,[12] only a very particular γ-selective Mannich-initiated cascade reaction has been described.[13] However, a direct catalytic asymmetric γ-regioselective vinylogous Mannich reaction involving acyclic enals to give δ-amino-α,β-unsaturated aldehydes has not been yet described.

In principle, a vinylogous extension of recently reported enantioselective α-alkylations of aldehydes with N-acyl quinolinium ions poses several reactivity and selectivity issues.[14-17] In fact, there are several regioselectivity issues about the nucleophilic addition (α-selectivity vs γ-selectivity) of the in situ formed dienamine to the reactive positions of the N-acylquinolinium ion (α′-selectivity vs γ′- selectivity) (Figure 1).[18] Moreover, the influence and sense of the asymmetric induction imposed by the chiral secondary amine catalyst in S_N-type γ-functionalizations are particularly intriguing given the distance of the chiral centres of the organocatalyst from the reactive remote γ-position. In particular, the reactive configuration of the second double bond in dienamine catalysis ("*E/Z*-dilemma") using acyclic aldehydes is still under dispute, and experimental insights useful for the comprehension of this problem are very limited. Recently, NMR and computational studies have been reported by Gschwind et al using Michler's hydrol as a model electrophile by dienamine activation of linear aldehydes with formation of one chiral centre.[19]

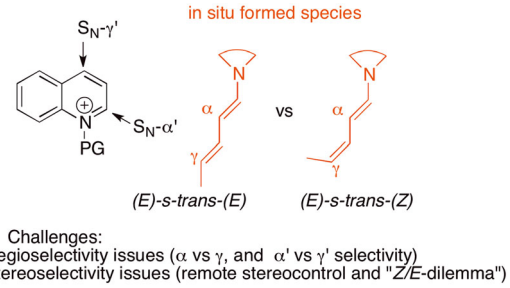


FIGURE 1 Different reactivity pathways of dienamine intermediates with a N-acylquinolinium ion

We now report the direct γ-regioselective functionalization of acyclic enals with in situ generated N-acyl quinolinium ions using dienamine catalysis with formation of two stereocentres for each reaction pathway (S_N-α′ and S_N-γ′).

2 | MATERIALS AND METHODS

2.1 | General

All reagents were purchased from commercially available sources. Compounds **1a,b** and have been prepared by known procedures.[14-16] For the preparation of other N,O-acetals, see ESI. Tetrahydrofuran (THF) and toluene were distilled on sodium/benzophenone ketyl. Solvents for extraction and chromatography were distilled before use. Analytical thin layer chromatography (TLC) was performed on silica gel on TLC Al foils (Sigma-Aldrich) with detection by exposure to ultraviolet light (254 nm) and/or by immersion in an acidic staining solution of *p*-anisaldehyde in EtOH. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Semipreparative TLC was performed on Merck PLC silica gel 60. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker Avance II 250 MHz spectrometer. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (chloroform-d: δ 7.26). Signal patterns are indicated as follows: br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Coupling constants (J) are given in hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded at 62.5 MHz with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (chloroform-d: δ 77.16). Electronic circular dichroism (ECD) spectra were recorded on a Jasco J-715 spectropolarimeter with 0.01-cm cells on acetonitrile solutions ca. 3.8 mM in the range 200 to 400 nm with the following conditions: scanning speed, 100 nm min^{-1}; step size, 0.1 nm; bandwidth, 2 nm, response time, 1 second; and accumulation of 24 scans. Melting points were determined on a Kofler apparatus and are uncorrected. High-resolution electrospray ionization mass spectrometry (HRESIMS) was acquired in positive ion mode with a Q-TOF premier spectrometer (Waters-Milford). Analytical high performance liquid chromatography (HPLC) was performed on a Waters 600E equipped with Varian Prostar 325 detector using a Daicel Chiralpak AD-H (250 × 4.6 mm) columns with detection at 220 nm.

Computational Section (see Supporting Information for details).

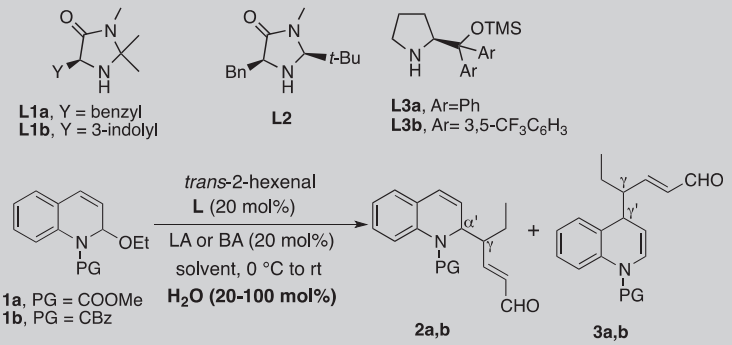
2.2 | Optimized procedure for vinylogous Mannich reaction

A 7-mL oven-dried pyrex vial was charged with 1.0 equivalent of the specified N,O-acetal in dry toluene (0.2 M). Subsequently, organocatalyst **L3b** (20 mol%), the α,β-unsaturated aldehyde (300 mol%), and H_2O (40 mol%) were added in this order. The reaction mixture was cooled at 0°C, and $In(OTf)_3$ (20 mol%) was added. The reaction mixture was allowed to react at room temperature until complete conversion of N,O-acetal (TLC detection). The reaction mixture was quenched by the addition of H_2O (3.0 mL) and the aqueous layer extracted with diethyl ether. The organic phase was dried on $MgSO_4$, filtered and concentrated in vacuum, and then purified by semi-preparative TLC or flash chromatography.

2.3 | Methyl (*E*)(2*R**)-2-((4*R*)1-oxohex-2-en-4-yl)quinoline-1(2*H*)-carboxylate (2a-*syn, anti*) (Entry 10, Table 1)

According to the general procedure, methyl-2-methoxyquinoline-1(2*H*)-carboxylate (35.0 mg, 0.15 mmol), *trans*-2-hexenal (45.0 mg, 0.45 mmol, 98%), **L3b** (18.5 mg, 0.03 mmol, 97%), In $(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) were allowed to react for 2 hours. Subsequent flash chromatography (hexanes/Et_2O 7:3, R_f = 0.13) afforded 16 mg (36% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.34 (d, *J* = 8.0 Hz, 0.4H, CHO *anti*); 9.20 (d, *J* = 7.9 Hz, 0.6H, CHO *syn*); 8.48 to 7.40 (m, 1H, Ar—H); 7.25 to 7.03 (m, 3H, Ar—H); 6.57 (d, *J* = 9.6 Hz, 1H, H_4); 6.46 (dd, *J* = 15.7, 9.7 Hz, 1H, $H_{3'}$); 6.11 (dd, *J* = 9.5, 6.0 Hz, 0.5H, H_3); 6.01 to 5.81 (m, 1.5H, H_3, $H_{2'}$); 5.10 (t, *J* = 6.9 Hz, 1H, H_2); 5.10 (t, *J* = 6.9 Hz, 1.8H,

TABLE 1 Screening of organocatalysts and reaction conditions in the model reaction[a]



Entry[a]	L	Solv	t[h]	2/3/Q[b]	dr[b] Anti/Syn	*ee*[%][c]
1[d]	**L1a**	THF	2	**Q** > 95	Nd	Nd
2[d]	**L2**	THF	2	**Q** > 85	Nd	Nd
3[d]	**L3a**	Toluene	18	**Q** > 95	Nd	Nd
4[d]	**L3b**	Toluene	18	**Q** > 85	Nd	Nd
5[e]	**L2**	THF	1	**70/23/7**	38/62	2/8
6[f]	**L2**	THF	1	12/11/77	31/69	4/6
7[e]	**L1a**	THF	12	27/16/57	38/62	10/20
8[e]	**L1b**	THF	12	22/11/67	35/65	12/32
9[e]	**L3a**	Toluene	18	10/5/85	Nd	Nd
10[e]	**L3b**	Toluene	2	56/36/8	60/40	65/6
11[e,g]	**L3b**	Toluene	2	56/36/8	57/43	72/23
12[g,h]	**L3b**	Toluene	3	50/35/15	58/42	79/12
13[g,i]	**L3b**	Toluene	48	52/34/14	56/44	77/35
14[g,j]	**L3b**	Toluene	3	**57/33/10**	**60/40**	**83/26**

[a]Unless stated otherwise, all reactions were carried out at 0°C using 0.20 mmol of **1a**, $In(OTf)_3$ (0.04 mmol), organocatalyst (0.04 mmol), 2-hexenal (0.6 mmol), solvent (0.4 mL) up to complete conversion (TLC analysis).

[b]Determined by ^1H NMR of the crude mixture on compounds of type **2**.

[c]Enantioselectivity of diastereoisomers of α,α′ adducts determined by HPLC on a chiral stationary phase.

[d]Reaction carried out in strictly anhydrous conditions.

[e]Reaction carried out with 100 mol% of H_2O.

[f]Reaction carried out with 0.2 mL of H_2O.

[g]Reaction carried out with **1b**.

[h]BA = 20 mol% of TsOH-H_2O.

[i]BA = anhydrous TsOH.

[j]Reaction carried out with 20 mol% of In $(OTf)_3$ and 40 mol% of H_2O.

$NCOOCH_3$*syn*); 3.75 (s, 1.2H, $NCOOCH_3$*anti*); 2.50 to 2.27 (m, 1H, $H_{4'}$); 1.77 to 1.34 (m, 2H, $H_{5'}$); 0.88 to 0.77 (m, 3H, $H_{6'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.7, 193.6, 158.4, 134.8, 134.5, 129.1, 128.4, 127.9, 127.1, 126.9, 125.2, 125.0, 122.1, 121.9, 111.6, 110.0, 53.5, 52.7, 52.1, 42.9, 42.5, 24.1, 23.9, 12.3, 12.2. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{17}H_{19}NO_3Na$ 308.1257, found 308.1255. The ee's were determined by Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 92:8) flow rate 1.0 ml/min; 220 nm: *syn*: t_r (major): 15.28 min, t_r (minor): 15.68 min; *anti*: t_r (major): 18.10 min, t_r (minor): 18.84 min.

2.4 | Benzyl (*E*)(2*S*)-2-((4*R*)1-oxohex-2-en-4-yl)quinoline-1(2*H*)-carboxylate (2b-*syn*) (Entry 14, Table 1)

According to the general procedure, benzyl-2-methoxyquinoline-1(2*H*)-carboxylate (35.0 mg,

0.15 mmol), *trans*-2-hexenal (45.0 mg, 0.45 mmol, 98%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) were allowed to react for 3 hours. Subsequent semipreparative TLC (hexanes/Et_2O 6:4, 3 runs, $R_f = 0.40$) afforded 8.1 mg (15% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.10 (d, J = 7.6 Hz, 1H, CHO); 7.33 (d, J = 8.0 Hz, 1H, Ar—H); 7.29 to 6.94 (m, 8H, Ar—H); 6.51 (d, J = 9.6 Hz, 1H, H_4); 6.41 (dd, J = 15.6, 9.6 Hz, 1H, $H_{3'}$); 6.09 (dd, J = 9.6, 6.0 Hz, 1H, H_3); 5.68 (dd, J = 15.6, 7.6 Hz, 1H, $H_{2'}$); 5.10 (d, J = 3.3 Hz, 2H, $NCOOCH_3Ar$); 5.06 to 4.96 (m, 1H, H_2); 2.29 to 2.14 (m, 1H, $H_{4'}$); 1.66 to 1.30 (m, 2H, $H_{5'}$); 0.73 (t, J = 7.4 Hz, $3H_{6'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 194.4, 159.0, 135.2, 128.9, 128.6, 128.3, 128.2, 126.8, 126.5, 125.0, 68.4, 55.4, 50.2, 23.51, 12.0. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{23}H_{23}NO_3Na$ 384.1570, found 384.1571. The ee was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 92:8) flow rate 1.0 mL/min; 220 nm*:* t_r (minor): 12.61 minutes, t_r (major): 13.06 minutes.

2.5 | Benzyl (*E*)(2*R*)-2-((4*R*)1-oxohex-2-en-4-yl)quinoline-1(2*H*)-carboxylate (2b-*anti*) (Entry 14, Table 1)

The faster eluting fractions of the above chromatography (hexanes/Et_2O 6:4, 3 runs, R_f = 0.50) afforded 13.3 mg (27% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.18 (d, J = 7.8 Hz, 1H, CHO); 7.52 to 7.43 (m, 1H, Ar—H); 7.39 to 7.31 (m, 5H, Ar—H); 7.21 to 7.12 (m, 1H, Ar—H); 7.08 to 7.03 (m, 2H, Ar—H); 6.57 (d, J = 9.6 Hz, 1H, H_4); 6.45 (dd, J = 15.6, 9.7 Hz, 1H, $H_{3'}$); 6.00 to 5.88 (m, 2H, H_3, $H_{2'}$); 5.26 (ABq, J = 12.4 Hz, 2H, $NCOOCH_2Ph$); 5.12 (t, J = 6.6 Hz, 1H, H_2); 2.46 to 2.31 (m, 1H, $H_{4'}$); 1.75 to 1.57 (m, 1H, $H_{5'}$); 1.45 to 1.31 (m, 1H, $H_{5'}$); 0.79 (t, J = 7.4 Hz, 3H, $H_{6'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.3, 157.1, 135.9, 135.0, 128.6, 128.3, 128.0, 127.9, 127.3, 126.5, 126.2, 124.7, 68.0, 54.9, 49.7, 22.9, 11.5. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{23}H_{23}NO_3Na$ 384.1570, found 384.1569. The ee was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 92:8) flow rate 1.0 mL/min; 220 nm*:* t_r (minor): 14.27 minutes, t_r (major): 17.37 minutes.

2.6 | Benzyl (*E*)(3*S*)-2-((4*R*)6-oxopent-2-en-4-yl)quinoline-1(2*H*)-carboxylate (2c-*syn*)

According to the general procedure, benzyl-2-methoxyquinoline-1(2*H*)-carboxylate (35.0 mg, 0.15 mmol), *trans*-2-pentenal (39.8 mg, 0.45 mmol, 95%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) were allowed to react for 5 hours. Subsequent semipreparative TLC (hexanes/Et_2O 6:4, 4 runs, $R_f = 0.58$) afforded 4.7 mg (9% yield) of the title compound as an amorphous solid. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.21 (bs, 1H,CHO), 7.38 to 7.32 (m, 7H, Ar—H), 7.10 to 7.06 (m, 2H, Ar—H), 6.59 (d, J = 9.5 Hz, 1H, H_4) 6.71 to 6.50 (m, 1H, $H_{3'}$), 6.10 (dd, J = 9.5, 6.0 Hz, 1H, H_3), 5.85 (dd, J = 15.6, 7.9, 1H, $H_{2'}$), 5.25 (d, J = 13.8 Hz, 2H, $NCOOCH_2Ar$), 4.99 (t, J = 7.7 Hz, 1H, H_2), 2.62 to 2.45 (m, 1H, $H_{4'}$), 1.11 (d, J = 6.7 Hz, 3H, $H_{5'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ ppm: δ 193.9, 159.1, 158.4, 136.1, 134.5, 133.5, 133.1, 128.8, 128.5, 128.2, 128.1, 127.5, 126.6, 126.4, 125.1, 124.9, 68.1, 55.9, 41.5, 15.5. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{22}H_{21}NO_3Na$ 370.1414, found 370.1415. The ee (23%) was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 95:5) flow rate 0.8 mL/min; 220 nm*:* t_r (minor): 15.61 minutes, t_r (major): 22.81 minutes.

2.7 | Benzyl (*E*)(3*R*)-2-((4*R*)6-oxopent-2-en-4-yl)quinoline-1(2*H*)-carboxylate (2c-*anti*)

The faster eluting fractions (hexanes/Et_2O 6:4, 4 runs, R_f = 0.65) afforded 6.3 mg (12% yield) of the title compound as a white solid. Mp: 99°C to 102°C. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.27 (d, J = 7.8 Hz, 1H, CHO); 7.56 to 7.47 (m, 1H, Ar—H); 7.41 to 7.31 (m, 5H, Ar—H); 7.24 to 7.15 (m, 1H, Ar—H); 7.11 to 7.06 (m, 2H, Ar—H); 6.65 (dd, J = 15.6, 8.3, 1H, $H_{3'}$); 6.58 (d, J = 10.3 Hz, 1H, H_4); 6.06 to 5.92 (m, 2H, $H_{2'}$ + H_3); 5.26 (ABq, J = 12.3 Hz, 2H, $NCOOCH_2Ph$); 5.03 (t, J = 7.0 Hz, 1H, H_2); 2.68 to 2.51 (m, 1H, $H_{4'}$); 1.07 (d, J = 6.8 Hz, 3H, $H_{5'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.6, 158.3, 133.3, 128.6, 128.3, 128.0, 127.9, 126.5, 126.3, 124.7, 68.0, 55.7, 41.9, 30.9, 15.3. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{22}H_{21}NO_3Na$ 370.1414, found 370.1414.The ee (72%) was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 95:5) flow rate 0.8 mL/min; 220 nm*:* 17.96 minutes, t_r (major): 19.47 minutes.

2.8 | Methyl (*E*)(3*R**)-2-((4R)1- oxodec-2-en-4-yl)quinoline-1(2*H*)-carboxylate (2d-*syn,anti*)

According to the general procedure, methyl-2-methoxyquinoline-1(2*H*)-carboxylate (35.0 mg, 0.15 mmol), *trans*-2-decenal (73.1 mg, 0.45 mmol, 95%), **L3b** (18.5 mg, 0.03 mmol, 97%), In $(OTf)_3$ (16.9 mg,

0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) were allowed to react for 5 hours. Subsequent semipreparative TLC (hexanes/AcOEt 9:1, four runs $R_f = 0.32$) afforded 20.2 mg (45% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.33 (d, $J = 7.9$ Hz, 0.55H, CHO *anti*); 9.17 (dd, $J = 7.8$, 2.1 Hz, 0.45H, CHO *syn*); 7.47 to 7.32 (m, 1H, Ar—H); 7.25 to 7.14 (m, 1H, Ar—H); 7.11 to 7.03 (m, 2H, Ar—H); 6.56 (d, $J = 9.7$, 2.8 Hz, 1H, H_4); 6.53 to 6.39 (m, 1H,),6.11 (dd, $J = 9.5$, 6.0 Hz, 0.57H *anti*), 6.01 to 5.79 (m, 1.5H), 5.13 to 4.99 (m, 1H, H_2), 3.82 (s, 1.35H, $NCOOCH_3$ *syn*), 3.75 (s, 1.65H, $NCOOCH_3$ *anti*), 2.52 to 2.31 (m, 1H, $H_{4'}$), 1.59 to 1.12 (m, 10H, $H_{5'}$, $H_{6'}$, $H_{7'}$, $H_{8'}$, $H_{9'}$), 0.86 (q, $J = 7.0$ Hz, 3H, $H_{10'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.8, 193.4, 158.4, 157.5, 155.2, 135.0, 134.6, 128.1, 128.0, 127.7, 127.4, 126.7, 126.4, 126.3, 125.2, 124.9, 124.8, 55.2, 54.9, 53.3, 48.2, 48.0, 32.0, 31.7, 30.2, 30.0, 29.8, 29.4, 29.2, 27.5, 27.0, 22.7, 14.2. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{21}H_{27}NO_3Na$ 364.1883, found 364.1880. The ee's were determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 96:4) flow rate 0.8 mL/min; 220 nm; *syn*: t_r (minor): 7.70 minutes, t_r (major): 8.24 minutes; *anti*: t_r (minor): 8.87 minutes, t_r (major): 10.97 minutes.

2.9 | Methyl (*E*)(3*R**)-2-((4*R*)1-oxohept-2-en-4-yl)quinoline-1(2*H*)-carboxylate (2e-*syn,anti*)

According to the general procedure, methyl-2-methoxyquinoline-1(2*H*)-carboxylate (35.0 mg, 0.15 mmol), *trans*-2-heptenal (52.03 mg, 0.45 mmol, 97%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 3 hours. Subsequent semipreparative TLC (hexanes/AcOAt 9:1, three runs $R_f = 0.21$) afforded 18 mg (40% yield) of the title compounds as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.32 (d, $J = 7.9$ Hz, 0.55H CHO *anti*); 9.16 (d, $J = 7.9$ Hz, 0.45H CHO *syn*); 7.45 to 7.34 (m, 1H, Ar—H); 7.24 to 7.13 (m, 1, Ar—H); 7.11 to 7.03 (m, 2H, Ar—H); 6.56 (d, $J = 9.6$ Hz, 1H, H_4); 6.45 (dd, $J = 15.9$, 9.8 Hz, $1H_{3'}$); 6.11 (dd, $J = 9.5$, 6.0 Hz, 0.5H, H_3); 6.01 to 5.79 (m, 1.5H, H_3, $H_{2'}$); 5.07 (dd, $J = 12.2$, 6.2 Hz, 1H, H_2); 3.81 (s, 1.45H, $NCOOCH_3$ *syn*), 3.75 (s, 1.55H, $NCOOCH_3$ *anti*), 2.44 (dd, $J = 9.6$, 4.4 Hz, 1H, $H_{4'}$), 1.39 to 0.93 (m, 4H, $H_{5'}$, $H_{6'}$), 0.89 to 0.80 (m, 3H, $H_{7'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.7, 193.4, 158.3, 157.4, 134.8, 134.4, 128.0, 127.9, 127.6, 127.3, 126.5, 126.3, 126.2, 125.0, 124.8, 124.7, 55.0, 54.7, 53.3, 53.2, 47.8, 47.6, 32.2, 32.0, 20.6, 20.1, 14.0, 13.9. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{18}H_{21}NO_3Na$ 322.1414, found 322.1411.The ee was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 96:4) flow rate 1.0 mL/min; 220 nm: *diastereoisomer 1*: 25%, t_r (minor): 9.84 minutes, t_r (major): 10.26 minutes; *diastereoisomer 2*: 84%, t_r (minor): 11.13 minutes, t_r (major): 12.05 minutes.

2.10 | Ethyl (*E*)(3*R**)-2-((4*R*)1-oxohept-2-en-4-yl)6-methylquinoline-1(2H)-carboxylate (2f-*syn,anti*)

According to the general procedure, ethyl-2-ethoxy-6-methylquinoline-1(2*H*)-carboxylate (38.9 mg, 0.15 mmol), *trans*-2-heptenal (52.03 mg, 0.45 mmol, 97%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 5 hours. Subsequent semipreparative TLC (hexanes/AcOEt 8:2, two runs, $R_f = 0.46$) afforded 26.4 mg (54% yield) of the title compounds as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.35 (d, $J = 7.9$ Hz, 0.5H, CHO), 9.20 (d, $J = 7.9$ Hz, 0.5H, CHO), 7.40 to 7.28 (m, 1H, Ar—H), 7.07 to 6.95 (m, 1H, Ar—H) 6.92 to 6.83 (m, 1H, Ar—H), 6.66 to 6.41 (m, 1.5H), 6.16 to 6.02 (m, 0.5H), 6.00 to 5.79 (m, 1H), 5.05 (dd, $J = 13.8$, 7.3 Hz, 1H, H_2), 4.38 to 4.06 (m, 2H, $NCOOCH_2CH_3$), 2.57 to 2.18 (m, 4H, $H_{4'}$, Ar-CH_3), 1.83 to 1.00 (m, 7H, $H_{5'}$, $H_{6'}$, $NCOOCH_2CH_3$), 0.96 to 0.81 (m, 3H, $H_{7'}$).^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.9, 193.6, 159.7, 158.8, 157.8, 134.8, 134.5, 134.3, 134.2, 132.6, 128.7, 127.4, 127.2, 126.8, 126.8, 126.7, 126.5, 125.0, 124.7, 62.4, 62.3, 55.0, 54.7, 47.8, 47.8, 45.7, 45.5, 36.5, 33.7, 32.4, 32.1, 29.8, 29.3, 22.9, 21.0, 20.9, 20.7, 20.2, 14.6, 14.2, 14.0. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{25}NO_3Na$ 350.1727, found 350.1729. The ee determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 92:8) flow rate 0.5 mL/min; 220 nm: one diastereoisomer t_r (minor): 13.9 minutes, t_r (major): 14.6 minutes; the enantiomers of the other diastereoisomer gave a single peak at 13.3 minutes.

2.11 | Methyl (*E*)(3*R**)-2-((4*R*)1-oxohept-2-en-4-yl)6-bromoquinoline-1(2*H*)-carboxylate (2g-*syn,anti*)

According to the general procedure, methyl-2-methoxy-6-bromoquinoline-1(2*H*)-carboxylate (44.5 mg, 0.15 mmol), *trans*-2-heptenal (52.03 mg, 0.45 mmol, 97%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 5.5 hours. Subsequent semipreparative TLC (hexanes/AcOEt 7:3, two runs, $R_f = 0.58$) afforded 42.4 mg (75% yield) of the title compounds as an amorphous solid.

^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.39 (d, J = 7.9 Hz, 0.5H, CHO *anti*), 9.26 (d, J = 7.8 Hz, 0.5H, CHO *syn*), 7.38 to 7.14 (m, 3H, Ar—H), 6.61 to 6.40 (m, 2H, H_4, $H_{3'}$), 6.17 (dd, J = 9.6, 6.0 Hz, 0.5H, H_3), 6.06 to 5.90 (m, 1H, H_3, $H_{2'}$), 5.85 (dd, J = 15.6, 8.0 Hz, 0.5H, $H_{2'}$), 5.12 to 4.97 (m, 1H, H_2), 3.82 (s, 1.5H, $NCOOCH_3$), 3.75 (s, 1.5H, $NCOOCH_3$), 2.53 to 2.29 (m, 1H, $H_{4'}$), 1.73 to 1.06 (m, 4H, $H_{5'}$, $H_{6'}$), 0.85 (t, J = 7.28 Hz, 1.5H, $H_{7'}$), 0.84 (t, J = 7.42 Hz, 1.5H, $H_{7'}$).^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.6, 193.3, 158.0, 156.9, 135.2, 134.8, 134.0, 133.4, 130.8, 129.4, 129.2, 129.0, 129.0, 128.2, 126.7, 126.4, 125.5, 125.4, 117.6, 55.2, 54.8, 53.6, 53.5, 47.8, 47.8, 32.2, 32.1, 29.8, 29.5, 22.8, 20.7, 20.2, 14.1, 14.0. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{18}H_{20}BrNO_3Na$ 400.0519, found 400.0517. The ee's were determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 96:4) flow rate 1.0 mL/min; 220 nm*; diastereomer 1*: 42% ee t_r (minor): 10.94 minutes, t_r (major): 10.26 minutes; *diastereomer 2:* 33% ee, t_r (minor): 10.83 minutes, t_r (major): 12.00 minutes.

2.12 | Ethyl (*E*)(3*R**)-2-((4*R*)1-oxohept-2-en-4-yl)6-methoxyquinoline-1(2*H*)-carboxylate (2h-*syn,anti*)

According to the general procedure, ethyl-2,6-dimethoxyquinoline-1(2*H*)-carboxylate (39.5 mg, 0.15 mmol), *trans*-2-heptenal (52.03 mg, 0.45 mmol, 97%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 4 hours. Subsequent semipreparative TLC (hexanes/AcOEt 7:3, one run, R_f = 0.28) afforded 25.5 mg (50% yield) of the title compounds as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.34 (d, J = 7.9 Hz, 0.6H, CHO *anti*), 9.23 (d, J = 7.9 Hz, 0.4H, CHO *syn*), 8.04 to 7.74 (m, 3H, Ar—H), 6.52 (d, J = 9.5 Hz, 1H, H_4), 6.65 to 6.42 (m, 2H, olefinic protons), 6.02 to 5.79 (m, 1H, olefinic proton), 5.12 to 4.93 (m, 1H, H_2); 4.35 to 4.06 (m, 2H, $NCOOCH_2CH_3$), 3.79 (s, 3H, Ar—OCH_3); 2.54 to 2.27 (m, 1H, $H_{4'}$), 1.68 to 1.04 (m, 4H, $H_{5'}$, $H_{6'}$), 0.85 (t, J = 7.38, 0.6H, $H_{7'}$ *anti*), 0.84 (t, J = 7.38, 0.4H, $H_{7'}$ *syn*).^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.9, 193.6, 162.9, 158.6, 157.8, 156.5, 156.5, 134.8, 134.5, 129.3, 129.1, 128.6, 128.4, 128.2, 126.6, 126.5, 126.0, 113.6, 113.5, 111.0, 111.0, 62.4, 62.3, 55.6, 55.0, 54.7, 47.7, 44.4, 32.4, 32.2, 29.8, 27.5, 20.7, 20.2, 14.6, 14.1, 14.0. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{25}NO_4Na$ 366.1676, found 366.1780. The ee's were determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 96:4) flow rate 1.0 mL/min; 220 nm*; syn* 11% ee, t_r (minor): 10.00 minutes, t_r (major): 12.24 minutes; *anti*: 40% ee, t_r (minor): 13.57 minutes, t_r (major): 15.72 minutes.

2.13 | Methyl (*E*)(3*R**)-2-((4*R*)1-oxohept-2-en-4-yl)4,7-dichloroquinoline-1(2*H*)-carboxylate (2i-*syn,anti*)

According to the general procedure, methyl-4,7-dichloro-2-ethoxyquinoline-1(2*H*)-carboxylate (45.1 mg, 0.15 mmol), *trans*-2-heptenal (52.03 mg, 0.45 mmol, 97%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 28 hours. Subsequent semipreparative TLC (hexanes/AcOEt 8:2, three runs, R_f = 0.4) afforded 17.4 mg (32% yield) of the title compounds as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.38 (d, J = 7.8 Hz, 0.40H, CHO *anti*), 9.26 (d, J = 7.7 Hz, 0.60H, CHO s*yn*), 7.57 to 7.37 (m, 2H), 7.21 to 7.11 (m, 1H), 6.47 (dd, J = 15.6, 6.5 Hz, 1H, $H_{3'}$), 6.24 (d, J = 6.7 Hz, 0.40H, H_3 *anti*), 6.11 (d, J = 6.6 Hz, 0.60H, H_3 *syn*), 5.98 (dd, J = 14.3, 6.4 Hz, 0.60H, $H_{2'}$ *syn*), 5.89 (dd, J = 15.38, 8.4 Hz, 0.40 H, $H_{2'}$ *anti*), 5.17 to 5.08 (m, 1H, H_2), 3.85 (s, 1.80H, $NCOOCH_3$ *syn*), 3.79 (s, 1.20H, $NCOOCH_3$ *anti*), 2.53 to 2.28 (m, 1H, $H_{4'}$), 1.27 to 1.24 (bs, 4H, $H_{5'}$, $H_{6'}$), 0.89 to 0.83 (m, 3H, H7′).^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.4, 193.0, 157.1, 155.9, 154.5, 135.4, 135.1, 134.9, 125.8, 125.7, 125.3, 125.2, 125.0, 124.8, 124.5, 124.1, 56.3, 56.0, 53.9, 47.8, 47.6, 45.7, 32.2, 32.1, 29.8, 22.8, 20.6, 20.1, 14.1, 14.0. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{20}H_{25}Cl_2NO_3Na$ 390.0634, found 390.0629. The ee was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 92:8) flow rate 0.5 mL/min; 220 nm; one diastereoisomer: t_r (minor): 8.7 minutes, t_r (major): 9.0 minutes.

2.14 | Methyl (*E*)(3*S*)-2-((4*R*)1-oxohept-2-en-4-yl)4-bromoquinoline-1(2*H*)-carboxylate (2j-*syn*)

According to the general procedure, methyl-4-bromo-2-methoxyquinoline-1(2*H*)-carboxylate (74.5 mg, 0.25 mmol), *trans*-2-heptenal (115.7 mg, 0.75 mmol, 95%), **L3b** (29.9 mg, 0.05 mmol, 97%), $In(OTf)_3$ (28.1 mg, 0.05 mmol), H_2O (1.8 μL, 0.10 mmol), and toluene (1.0 mL) reacted for 2 hours. Subsequent semipreparative TLC (hexanes/AcOEt 8:2, three runs, R_f = 0.46) afforded 20 mg (21% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.18 (d, J = 7.8 Hz, 1H, CHO); 7.55 (d, J = 7.7 Hz, 1H, Ar—H); 7.46 to 7.11 (m, 3H, Ar—H); 6.47 to 6.34 (m, 2H, $H_{3'}$ + H_3); 5.94 (dd, J = 15.5, 7.9 Hz, 1H, H_2); 5.08 (t, J = 6.9 Hz, 1H, H_2); 3.82 (s, 3H, $NCOOCH_3$); 2.57 to 2.39 (m, 1H, $H_{4'}$); 1.63 to 1.25 (m, 4H, $H_{5'}$ + $H_{6'}$); 0.84 (t, J = 6.69 Hz, 3H, $H_{7'}$).^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.1, 156.2, 135.0, 130.6, 129.4,

128.3, 126.8, 126.4, 125.0, 124.8, 119.8, 56.9, 53.5, 47.5, 32.0, 29.7, 20.0, 13.8. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{18}H_{20}BrNO_3Na$ 400.0519, found 400.0518. The ee (68%) was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 95:5) flow rate 0.8 mL/min; 220 nm: t_r (minor): 9.57 minutes, t_r (major): 11.67 minutes.

2.15 | Methyl (E)(3*R*)-2-((4*R*)1-oxohept-2-en-4-yl)4-bromoquinoline-1(2*H*)-carboxylate (2j-*anti*)

The slower eluting fractions of the above semipreparative TLC (hexanes/AcOEt 8:2, 3 runs, $R_f = 0.40$), afforded 17.2 mg (18% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.36 (d, J = 7.9 Hz, 1H, CHO); 7.56 (d, J = 7.7 Hz, 1H, Ar—H); 7.33 to 7.29 (m, 2H, Ar—H); 7.20 (d, J = 8.1 Hz, 1H, Ar—H); 6.49 (dd, J = 15.33, 5.99 Hz, 1H, $H_{3'}$); 6.51 (d, J = 6.6 Hz, 1H, H_3); 5.84 (dd, J = 15.5, 7.8 Hz, 1H, $H_{2'}$); 5.07 to 4.97 (m, 1H, H_2); 3.76 (s, 3H, $NCOOCH_3$); 2.42 (dd, J = 9.6, 3.8 Hz, 1H, $H_{4'}$); 1.43 to 1.10 (m, 4H, $H_{5'}$, $H_{6'}$); 0.86 (t, J = 7.2 Hz, 3H, $H_{7'}$).^{13}C-NMR (63 MHz, $CDCl_3$) δ: ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 144.5, 135.8, 130.4, 127.9, 127.5, 126.3, 59.5, 57.3, 54.3, 48.3, 33.3, 30.8, 21.6, 19.6, 14.9. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{18}H_{20}BrNO_3Na$ 400.0519, found 400.0519. The ee (45%) was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 95:5) flow rate 0.8 mL/min; 220 nm: t_r (minor): 8.08 minutes, t_r (major): 8.98 minutes.

2.16 | Benzyl (*E*)(3*S*)-2-((4*R*)1-oxohept-2-en-4-yl)4-bromoquinoline-1(2*H*)-carboxylate (2k-*syn*)

According to the general procedure, benzyl-4-bromo-2-methoxyquinoline-1(2*H*)-carboxylate (93.5 mg, 0.25 mmol), *trans*-2-heptenal (115.7 mg, 0.75 mmol, 95%), **L3b** (29.9 mg, 0.05 mmol, 97%), $In(OTf)_3$ (28.1 mg, 0.05 mmol), H_2O (1.8 μL, 0.10 mmol), and toluene (1.0 mL) reacted for 2.5 hours. Subsequent semipreparative TLC (hexanes/Et_2O 8:2, 4 runs, $R_f = 0.41$) afforded 5.1 mg (4.5% yield) of the title compound as unstable colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.28 (bs, 1H, CHO); 7.56 (d, J = 7.8 Hz, 1H, Ar—H); 7.39 to 7.28 (m, 7H, Ar—H); 7.19 (d, J = 7.9 Hz, 1H, Ar—H); 6.69 to 6.34 (m, 1H, $H_{3'}$); 6.50 (d, J = 6.7 Hz, 1H, H_3); 5.79 (dd, J = 15.5, 7.8 Hz, 1H, $H_{3'}$); 5.31 to 5.14 (m, 2H, $NCOOCH_3Ar$); 5.08 to 4.99 (m, 1H, H_2); 2.46 to 2.34 (m, 1H, $H_{4'}$); 1.71 to 1.20 (m, 4H, $H_{5'}$ + $H_{6'}$); 0.90 to 0.82 (m, 3H, $H_{7'}$).^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.5, 157.7, 152.0, 149.7, 145.0, 134.8, 129.5, 128.8, 127.1, 125.2, 68.3, 58.7, 56.6, 47.3, 32.3, 29.8, 20.6, 14.1. HRMS (ESI) m/z [M + Na^+] Calcd $C_{24}H_{24}BrNO_3Na$ 476.0832, found 476.0834. The ee (50%) was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 95:5) flow rate 0.8 mL/min; 220 nm: 13.12 minutes, t_r (major): 14.36 minutes.

2.17 | Benzyl (*E*)(3R)-2-((4*R*)1-oxohept-2-en-4-yl)4-bromoquinoline-1(2*H*)-carboxylate (2k-*anti*)

The slower eluting fractions of the above semipreparative TLC (hexanes/Et_2O 8:2, 4 runs, $R_f = 0.36$) afforded 6.8 mg (6% yield) of the title compound as unstable colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.16 (d, J = 7.8, Hz, 1H, CHO); 7.54 (dd, J = 7.7, 1.8 Hz, 1H, Ar—H); 7.39 to 7.33 (m, 7H, Ar—H); 7.15 (d, J = 7.4 Hz, 1H, Ar—H); 6.47 to 6.28 (m, 2H, $H_{3'}$ + H_3); 5.92 (dd, J = 15.6, 7.9 Hz, 1H, $H_{2'}$), 5.34 to 5.18 (m, 2H, $NCOOCH_2Ar$); 5.10 (t, J = 7.0 Hz, 1H, H_2); 2.44 to 2.37 (m, 1H, $H_{4'}$); 1.68 to 1.10 (m, 4H, $H_{5'}$, $H_{6'}$);0.80 (t, J = 8.1 Hz, 3H, $H_{7'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 201.9, 193.6, 193.1, 159.9, 156.2, 154.0, 135.0, 134.3, 129.4, 128.6, 128.4, 128.1, 126.8, 126.4, 125.0, 124.8, 119.8, 68.3, 56.9, 47.5, 32.0, 20.0, 14.0, 13.8. HRMS (ESI) m/z [M + Na^+] Calcd $C_{24}H_{24}BrNO_3Na$ 476.0832, found 476.0831. The ee (66%) was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 95:5) flow rate 0.8 mL/min; 220 nm: t_r (minor): 16.45 minutes, t_r (major): 20.40 minutes.

2.18 | Methyl (*Z*)-2-(1-(2-oxoethylidene)-1,2,3,4-tetrahydronaphthalen-2-yl) quinoline-1(2*H*)-carboxylate (2l)

According to the general procedure, methyl-2-methoxyquinoline-1(2*H*)-carboxylate (35.0 mg, 0.15 mmol), (*E*)-2-(3,4-dihydronaphthalen-1(2*H*)-yidene) acetaldehyde (77.5 mg, 0.45 mmol), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 3.5 hours. Subsequent semipreparative TLC (hexanes/EAcOEt 8:2, two runs, R_f = 0.23) afforded 12.8 mg (22% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.41 (d, J = 8.1 Hz, 1H, CHO); 7.59 (d, J = 7.8 Hz, 1H, Ar—H); 7.41 to 7.09 (m, 8H); 6.63 (d, J = 9.6 Hz, 1H); 6.46 (d, J = 8.1 Hz, 1H); 6.15 (dd, J = 9.6, 6.1 Hz, 1H), 5.11 (bs, 1H); 3.43 (s, 3H); 3.70 (dd, J = 10.2, 3.7 Hz, 1H); 3.20 to 2.86 (m, 2H); 2.47 to 1.75 (m, 3H). ^{13}C-NMR (63 MHz,

$CDCl_3$) δ: 192.1, 157.3, 155.9,131.7, 130.5, 128.5,128.2, 127.3, 127.2, 126.3, 126.3, 126.0, 54.0, 51.3 (C5), 36.5, 25.1, 24.5.HRMS (ESI) m/z [M + Na^+] Calcd for $C_{24}H_{23}NO_3Na$ 396.1570, found 396.1570. The ee (81%) was determined with Daicel Chiralcel AD-H column (heptane–*i*-PrOH, 95:5) flow rate 0.8 ml/min; 220 nm: t_r (minor): t_r (minor): 41.77 minutes, t_r (major): 46.14 minutes.

2.19 | Methyl (*E*)(4*R**)-4-((4*R*)1-oxohex-2-en-4-yl)quinoline-1(4*H*)-carboxylate (3a-*syn,anti*)

According to the general procedure, 2-methoxyquinoline-1(2*H*)-carboxylate (35 mg, 0.15 mmol), *trans*-2-hexenal (45.0 mg, 0.45 mmol, 98%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 2 hours. Subsequent flash chromatography (hexanes/Et_2O 7:3, R_f = 0.25) afforded 10 mg (23% yield) of the title compounds as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.33 (d, *J* = 7.8 Hz, 0.5 H, CHO), 9.30 (d, *J* = 7.8 Hz, 0.5 H, CHO), 7.87 (dd, *J* = 12.9, 8.2 Hz, 1H, H_2), 7.19 (m, 4H, Ar—H), 6.44 (dd, 1H, *J* = 15.7, 9.4 Hz, $H_{3'}$), 5.93 (m, 1H, $H_{2'}$), 5.33 (dd, 1H *J* = 7.8, 6.2 Hz, H_3), 3.82 (s, 1.5H, $COOCH_3$), 3.86 (s, 1.5H, $COOCH_3$), 3.55 (m, 1H, H_4), 2.38 (dd, *J* = 14.0, 9.5 Hz, 1H, $H_{4'}$), 1.73 to 1.45 (m, 1H, $H_{5'}$), 0.85 (t, *J* = 7.4 Hz, 1.5H), 0.90 (t, *J* = 7.3 Hz, 1.5H). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.7, 193.6, 153.0, 158.4, 134.8, 134.5, 129.1, 128.4, 127.9, 127.1, 122.1, 121.9, 111.6, 110.0, 53.6, 52.7, 52.1, 42.9, 42.5, 24.1, 23.9, 12.3, 12.2. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{23}H_{23}NO_3Na$ 308.1257, found 308.12576.

2.20 | Benzyl (*E*)(4*R**)-4-((4*R*)1-oxohex-2-en-4-yl)quinoline-1(4*H*)-carboxylate (3b-*syn,anti*)

According to the general procedure, benzyl-2-methoxyquinoline-1(2*H*)-carboxylate (35 mg, 0.15 mmol), *trans*-2-hexenal (45.0 mg, 0.45 mmol, 98%), **L3b** (18.5 mg, 0.03 mmol, 97%), $In(OTf)_3$ (16.9 mg, 0.03 mmol), H_2O (1.1 μL, 0.06 mmol), and toluene (0.6 mL) reacted for 3 hours. Subsequent semipreparative TLC (hexanes/Et_2O 6:4, 3 runs, R_f = 0.60) afforded 8.9 mg (12.4% yield) of the title compound as a colourless oil. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.33 (d, *J* = 7.8 Hz, 0.5H, CHO); 9.20 (d, *J* = 7.8 Hz, 0.5H, CHO); 7.93 (d, *J* = 8.3 Hz, 0.5H, H_2); 7.88 (d, *J* = 8.3 Hz, 0.5H, H_2) 7.44 to 7.02 (m, 9H, Ar—H); 6.56 (dd, *J* = 15.1, 9.3 Hz, 1H, 0.5 H, $H_{3'}$); 6.38 (dd, *J* = 15.5, 9.6 Hz, 0.5H, $H_{3'}$); 6.03 (dd, *J* = 15.6, 7.8 Hz, 0.5H, $H_{2'}$); 5.83 (dd, *J* = 15.7, 7.8 Hz, 0.5H,$H_{2'}$). ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 193.5, 193.4, 158.3, 158.1, 152.1, 135.7, 128.8, 126.0, 128.3, 127.7, 126.8, 126.7, 126.4, 125.1, 124.8, 121.8, 121.7, 111.3, 110.0, 68.2, 52.5, 52.0, 42.7, 42.1, 24.0, 23.5, 12.1, 12.0. HRMS (ESI) m/z [M + Na^+] Calcd for $C_{23}H_{23}NO_3Na$ 384.1570, found 384.1573.

3 | RESULTS AND DISCUSSION

At the outset, in order to explore the regioselectivity and stereoselectivity of the reaction of in situ formed dienamines with N-acylquinolinium ions, *trans*-2-hexenal was allowed to react with N,O-acetal **1a** in the presence of catalytic amounts (20 mol%) of MacMillan (**L1a**,**L2**) or Hayashi-Jørgensen (**L3a,b**) organocatalysts, and $In(OTf)_3$ in anhydrous THF or toluene, respectively (Scheme Table 1). This choice of solvents proved to be optimal in terms of yield and enantioselectivity for related α-alkylations.[14] After complete conversion of **1a,** only trace amounts of regioisomeric addition products **2a** (γ,α′) and **3a** (γ,γ′) were detected in the crude mixture, with quinoline (**Q**) found as the major decomposition product (>85%, entries 1-4, Table 1). Much to our delight, *we found that the reaction carried out in the presence of stoichiometric amounts (100 mol%) of water* dramatically reduced the extent of decomposition to quinoline and delivered good yields of addition products **2a** and **3a**, albeit in a racemic fashion, in a very short reaction time (entry 5). On the other hand, the use of a large excess of water afforded compounds **2a** and **3a** with a lower efficiency (entry 6). The use of first generation MacMillan catalysts **L1a,b** gave a much slower reaction with a slightly improved enantioselectivity, but a consistent amount of quinoline was found (entries 7,8). Regioisomeric compounds of type **2** (γ,α′-addition) and of type **3** (γ,γ′-addition) turned out to be separable by silica gel chromatography (Table 1).

The high reactivity of organocatalyst **L2** in this vinylogous reaction was quite surprising considering that MacMillan imidazolidinones have a very weak preference for dienamine formation.[20] Interestingly, whilst prolinol aminocatalyst **L3a** afforded mainly the decomposition product (entry 9), the use of catalyst **L3b** gave a lower amount of quinoline with an increase of the enantioselectivity (entry 10). We then concentrated our optimization efforts on Cbz-protected quinoline N,O-acetal **1b**. In fact, with this substrate, the *syn,anti*-diastereoisomers of corresponding γ,α′-nucleophilic enal addition product **2b** turned out to be separable by silica gel chromatography (entries 11-14). The use of a strong Brønsted acid (BA) such as TsOH-H_2O was found

suitable to promote the reaction (entry 12). However, differently from the enantioselective α-alkylations of aldehydes,[14] anhydrous TsOH prolonged the reaction time (entry 13). The use of 20 mol% of $In(OTf)_3$ in the presence of 40 mol% of H_2O gave the best compromise between reactivity and enantioselectivity (entry 14). Even if the beneficial effect of measured amounts of water in our case has not been fully rationalized, its effect is likely related to an improvement in catalyst turnover during the hydrolysis of the final iminium ion (Scheme 1).[21,22]

After these preliminary results, we then applied the optimized reaction conditions making use of Hayashi-Jørgensen **L3b** to a broader range of enals and N-acylquinolinium ions, and the results are summarized in Scheme 1. It should be noted that the use of quinoline N,O-acetals containing more hindered protecting group (PG = COO*i*Pr, COO*t*Bu) in order to get an improved diastereoselectivity and or enantioselectivity was totally uneffective.[23] In general, the formation of two stereocenters was accomplished with moderate regioselectivity (γα′-γγ∋), low diastereoselectivity for both regioisomeric adducts, and good to high enantioselectivity at least for one diastereoisomer that is usually the *anti* one. α−Substituted and α,β-disubstituted acyclic aldehydes were found not reactive in our reaction conditions. The use of substituted dihydroquinolines was tolerated, but a drop in yields and enantioselectivity was generally observed (compounds **2f-k**). The use of substituent at the 4-position of the quinoline-N,O-acetal clearly avoided the formation of the regioisomeric γγ′-adduct but also caused a depletion of isolated yields (compounds **2j-k**). The highest enantioselectivity (96% ee for the major *anti*-diastereoisomer of **2d**) was obtained with 2-decenal.

It should be noted that similar embedment of α,β-unsaturated linear aldehydes at the 2-position of a tetrahydroquinoline has been previously obtained only

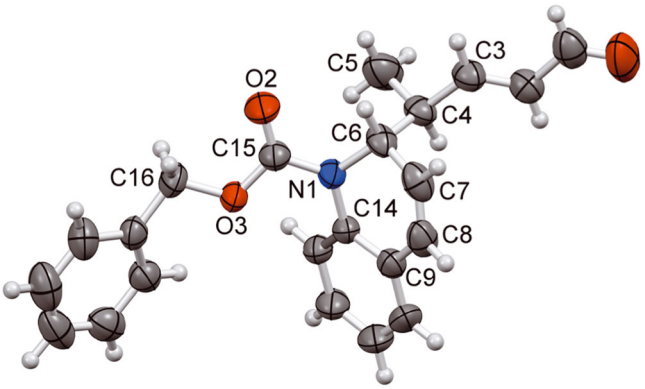
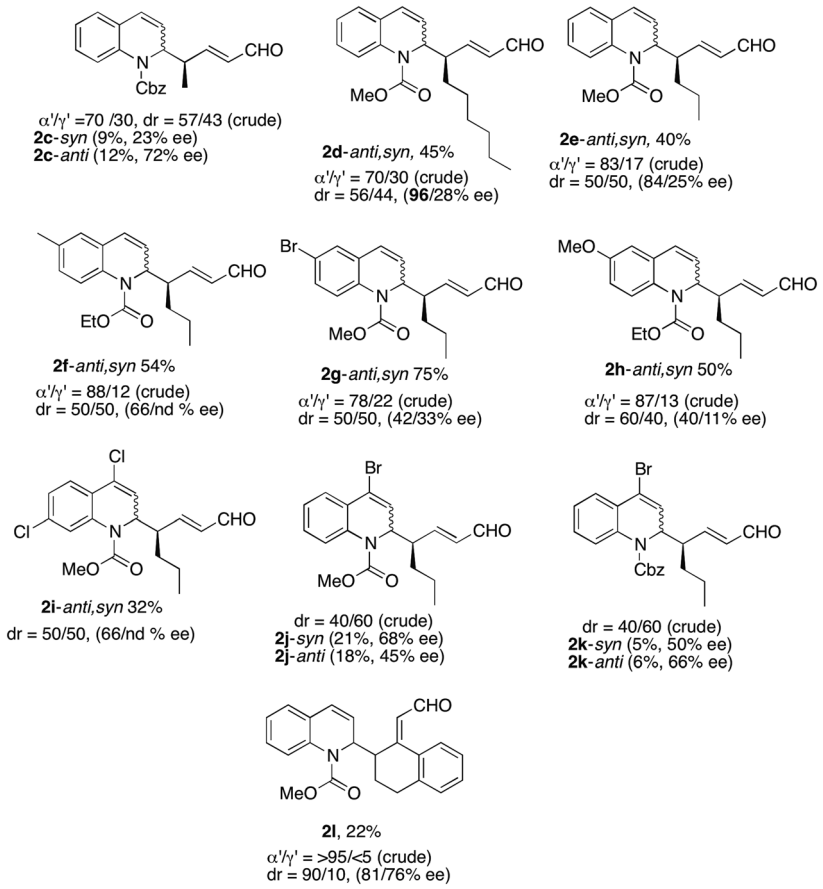


FIGURE 2 Molecular structure of **2c**-*anti*. Thermal ellipsoids are at 50% probability



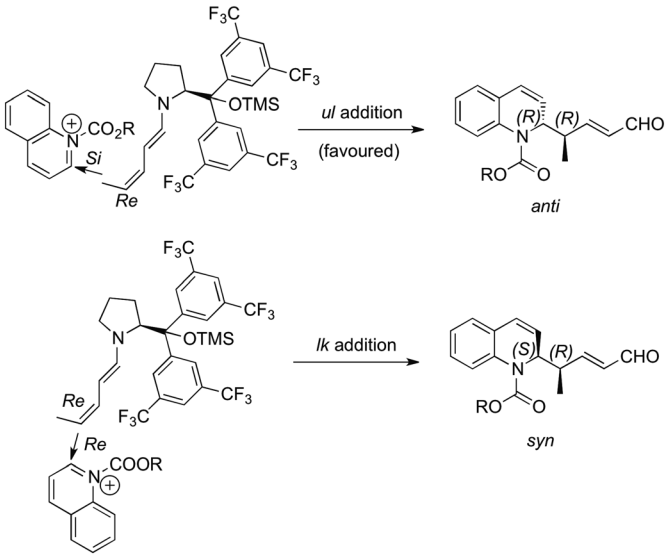
SCHEME 1 Scope of the vinylogous Mannich reaction with prolinol catalyst **L3b**

after very long synthetic procedures and in racemic form en route to compounds of pharmaceutical interest.[24] The only cyclic α,β-unsaturated aldehyde used with our protocol afforded the corresponding functionalized 1,2-dihydroquinoline **2l** with a high level of regioselectivity, diastereoselectivity, and enantioselectivity, albeit with a low isolated yield.

The determination of the relative and absolute configurations of 1,2-dihydroquinolines **2a-k** derived from acyclic enals was realized by the combination of several techniques. In particular, the relative configuration was determined on compound **2c**-*anti* by X-ray analysis (Figure 2).[25]

The diastereoisomeric nature of **2c**-*syn* was then confirmed by NMR. The absolute configuration of the endocyclic stereocentre was established as (*S*) for compound **2c**-*syn* and (*R*) for **2c**-*anti* by ECD.

Using a combined experimental and computational procedure, the ECD spectra of **2c**-*syn* and **2c**-*anti* were recorded in acetonitrile and compared with those calculated by density functional theory (DFT) on a truncated model of **2c** (benzyl of Cbz replaced by methyl).[26,27] As



SCHEME 2 Stereochemical models for main facial selectivity observed

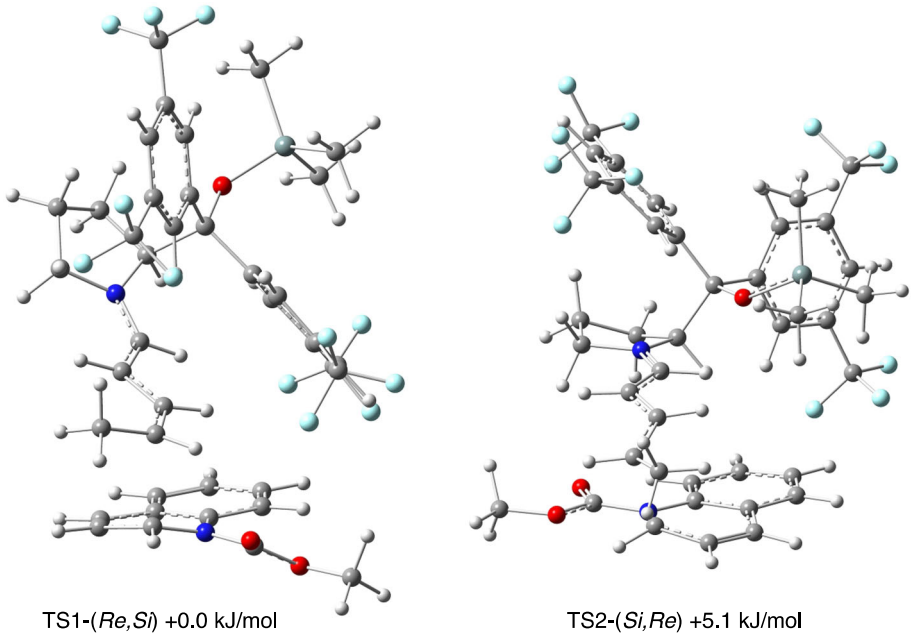


FIGURE 3 Transition states leading to (*R*,*R*) and (*S*,*S*)-*anti* diastereoisomers

recently observed for other 1,2-dihydroquinoline derivatives,[28] the ECD spectra of **2c** is dominated by the configuration of the endocyclic stereocentre. The configuration of the endocyclic stereocentre depends on the attack of the dienamine with either *Re* or *Si* face of the N-acyl quinolinium ion (Scheme 2). What is relevant for this work is the (*R*)-absolute configuration of the exocyclic stereocentre present in the major enantiomer of both compounds **2c**-*anti* (72% ee) and **2c**-*syn* (23% ee). As only one face is shielded by the substituent, the (*R*)-absolute configuration of the exocyclic stereocentre derives necessarily by the *ul* and *lk* addition, respectively, of the *Re* face of the second double bond of the corresponding dienamine in its (*E*)-s-*trans*-(*Z*) form, to the N-acyl quinolinium ion (Scheme 2).

The experimental data obtained throughout this work in which the (*R*,*R*)-*anti* diastereoisomer is the prevailing enantiomer are also supported by theoretical calculations (B3LYP-D3/def2-SVP).[27] These data have shown that TS1 leading to (*R*,*R*)-*anti*-diastereoisomeric adduct starting from a (*Z*)-configuration of the remote double bond is by 5.1 kJ/mol more favoured as compared with the TS2 leading to (*S*,*S*)-*anti*-diastereoisomer starting from *E*-configuration of the remote double bond (Figure 3). These results are in agreement with computational results obtained by Gschwind and coworkers where a kinetic preference for *Z* configuration of the second double bond was evidenced.[19] The facial selectivity of the only one chiral centre formed was rationalized by the authors in terms of advantageous CH-π interactions between (*E*)-*s*-*trans*-(*Z*)-dienamine and the electrophile.

4 | CONCLUSIONS

In conclusion, we have studied the direct functionalization of acyclic enals with in situ generated N-acyl quinolinium ions using dienamine catalysis with formation of two stereocentres. The activation of the enal proved to be completely γ-regioselective, but complex mixtures of products were generally obtained. MacMillan imidazolidinone **L2** showed to be unexpectedly reactive in the activation of enals by dienamine formation even if the corresponding products were obtained with a poor enantioselectivity. Several chiral nonracemic γ-dihydroquinolyl-substituted-α,β-unsaturated aldehydes have been obtained with moderate to good enantioselectivities, albeit with a generally poor diastereocontrol, using prolinol organocatalyst **L3b**. Our experimental and theoretical data corroborate the hypothesis according to which the remote S_N-type reactions of dienamines with large electrophiles occur mainly via a kinetic preference for the (*Z*)-form of the second double bond.

ACKNOWLEDGMENTS

We gratefully acknowledge the University of Pisa for financial support (P.R.A. 2016_27). G.P. acknowledges the CINECA award under the ISCRA initiative, for the availability of high performance computing resources and support. We also acknowledge Enrico Mazzoni and Giuseppe Terreni (INFN Sezione di Pisa) for the availability of additional computing resources.

ORCID

Lucilla Favero https://orcid.org/0000-0003-3178-7566
Valeria Di Bussolo https://orcid.org/0000-0001-6126-9984
Fabio Marchetti https://orcid.org/0000-0002-3683-8708
Gennaro Pescitelli https://orcid.org/0000-0002-0869-5076
Sebastiano Di Pietro https://orcid.org/0000-0003-3585-6573
Mauro Pineschi https://orcid.org/0000-0001-6063-2198

REFERENCES AND NOTES

1. Arceo E, Melchiorre P. Extending the aminocatalytic HOMO-raising activation strategy: where is the limit? *Angew Chem Int Ed*. 2012;51(22):5290-5291.
2. Casiraghi G, Zanardi F, Battistini L, Rassu G. Advances in exploring heterocyclic dienoxysilane nucleophiles in asymmetric synthesis. *Synlett*.2009;(10):1525-1542.
3. Gu Y, Wang Y, Yu TY, Liang YM, Xu PF. Rationally designed multifunctional supramolecular iminium catalysis: direct vinylogous Michael addition of unmodified linear dienol. *Angew Chem Int Ed*. 2014;53(53):14128-14131.
4. Donslund BS, Halskov KS, Leth LA, Matos Paz B, Jørgensen KA. Organocatalytic asymmetric strategies to carbocyclic structures by γ-alkylation-annulation sequences. *Chem Commun*. 2014;50(89):13676-13679.
5. deFigueiredo RM, Fröhlich R, Christmann M. Amine-catalyzed cyclizations of tethered α,β-unsaturated carbonyl compounds. *Angew Chem Int Ed*. 2008;47(8):1450-1453.
6. Volz N, Bröhmer MC, Nieger M, Bräse S. Thieme chemistry journal awardees—where are they now? An asymmetric organocatalytic sequence towards 4a-methyl tetrahydroxanthones: formal synthesis of 4-dehydroxydiversonol. *Synlett*. 2009;4:550-553.
7. Stiller J, Marqués-López E, Herrera RP, Fröhlich R, Strohmann C, Christmann M. Enantioselective α- and γ-alkylation of α,β-unsaturated aldehydes using dienamine activation. *Org Lett*. 2011;13(13):70-73.
8. Bergonzini G, Vera S, Melchiorre P. Cooperative organocatalysis for the asymmetric γ alkylation of α-branched enals. *Angew Chem Int Ed*. 2010;49(50):9685-9688.
9. Silvi M, Cassani C, Moran A, Melchiorre P. Secondary amine-catalyzed asymmetric γ-alkylation of α-branched

enals *via* dienamine activation. *Helv Chim Acta*. 2012;95(10):1985-2006.

10. Kutwal MS, Appayee C. Highly regio- and enantioselective γ-alkylation of linear α,β-unsaturated aldehydes. *Eur J Org Chem*.2017;(29):4230-4234.
11. Næsborg L, Halskov KS, Tur F, Mønsted SMN, Jørgensen KA. Asymmetric γ-allylation of α,β-unsaturated aldehydes by combined organocatalysis and transition-metal catalysis. *Angew Chem Int Ed*. 2015;54(35):10193-10197.
12. Bertelsen S, Marigo M, Brandes S, Dinér P, Jørgensen KA. Dienamine catalysis: organocatalytic asymmetric γ-amination of α,β-unsaturated aldehydes. *J Am Chem Soc*. 2006;128(39):12973-12980.
13. Ransborg LK, Overgaard M, Hejmanowska J, Barfüsser S, Jørgensen KA, Albrecht L. Asymmetric formation of bridged benzoxazocines through an organocatalytic multicomponent dienamine-mediated one-pot cascade. *Org Lett*. 2014;16(16):4182-4185.
14. Berti F, Malossi F, Marchetti F, Pineschi M. Highly enantioselective Mannich reaction of aldehydes with cyclic N-acyliminium ions by synergistic catalysis. *Chem Commun*. 2015;51(71):13694-13696.
15. Volla CMR, Fava E, Atodiresei I, Rueping M. Dual metal and Lewis base catalysis approach for asymmetric synthesis of dihydroquinolines and the α-arylation of aldehydes *via* *N*-acyliminium ions. *Chem Commun*. 2015;51(87):15788-15791.
16. Sun S, Mao Y, Lou H, Liu L. Copper (II)/amine synergistically catalyzed enantioselective alkylation of cyclic N-acyl hemiaminals with aldehydes. *Chem Commun*. 2015;51(53):10691-10694.
17. For a review on the use of N,O-acetals in asymmetric synthesis, see:Huang YY, Cai C, Yang X, Lv ZC, Schneider U. Catalytic asymmetric reactions with *N*,*O*-aminals. *ACS Catalysis*. 2016;6:5747-5763.
18. For a recent review about dienamine activation with enals, see: Marcos V, Alemán J. Old tricks, new dogs: organocatalytic dienamine activation of α,β-unsaturated aldehydes. *Chem Soc Rev*. 2016;45:6812-6832.
19. Seegerer A, Hioe J, Hammer MM, Morana F, Fuchs PJW, Gschwind RM. Remote-stereocontrol in dienamine catalysis: *Z*-dienamine preferences and electrophile–catalyst interaction revealed by NMR and computational studies. *J Am Chem Soc*. 2016;138(31):9864-9873.
20. For a very recent ^{1}H NMR study of dienamine formation, see: Lagiewka B, Albrecht L. Studies on the formation of dienamine and trienamine intermediates by ^{1}H NMR spectroscopy. *Asian J Org Chem*. 2017;6:516-519.
21. Giacalone F, Gruttadauria M. Water in organocatalytic reactions. In: Dalko PI, ed. *Comprehensive Enantioselective Organocatalysis*. Vol.II Wiley-VCH; 2013:673-717. https://doi.org/10.1002/9783527658862.ch24
22. For combinations of indium salts and water, see:Sinisi R, Vita MV, Gualandi A, Emer E, Cozzi PG. SN1-Type Reactions in the Presence of Water: Indium (III)-Promoted Highly Enantioselective Organocatalytic Propargylation of Aldehydes. *Chem A Eur J*. 2011;17:7404-7408. and references cited therein
23. It was not possible to obtain the quinoline N,O-acetal with Boc-protection. The quinoline N,O-acetal with PG = COO*i*Pr was prepared but it was found totally unreactive in our reaction conditions.
24. Scott JD, Miller MW, Li SW, et al. Tetrahydroquinoline sulfonamides as vasopressin 1b receptor antagonists. *Biorg Med Chem Lett*. 2009;19(21):6018-6022.
25. CCDC 1874936 contains the supplementary crystallographic data for compound **2c**-*anti*. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
26. Pescitelli G, Bruhn T. Good computational practice in the assignment of absolute configurations by TDDFT calculations of ECD spectra. *Chirality*. 2016;28(6):466-474.
27. See Supporting Information for details.
28. Menichetti A, Berti F, Guazzelli L, et al. Organocatalytic alkylation of carbohydrate-containing aldehydes with dihydroquinoline N,O-acetals: absolute configuration of 1,2-dihydroquinolines. *Chirality*. 2019;31(2):127-137.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Vargiu M, Favero L, Menichetti A, et al. Direct enantioselective vinylogous Mannich-type reactions of acyclic enals: New experimental insights into the *E/Z*-dilemma. *Chirality*. 2019;1–12. https://doi.org/10.1002/chir.23077