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A New Imidazole-Containing Imidazolidinone Catalyst for Organocatalyzed Asymmetric Conjugate Addition of Nitroalkanes to Aldehydes

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Abstract: Herein we report a new organocatalyst for the asymmetric Michael addition of nitroalkanes to α,β-unsaturated aldehydes. This catalyst incorporates a basic imidazole group in addition to the secondary amine responsible for activation of the α,β-unsaturated carbonyl compounds *via* iminium ion formation. The new organocatalyst is capable of catalyzing the enantioselective carbon-carbon bond formation with a high degree of enantiocontrol providing products in enantiomeric excesses of up to 92% and yields of up to to 91%. These results constitute the best results so far reported for organocatalyzed Michael additions of nitroalkanes to α,β-unsaturated aldehydes, and provide proof of principle that organocatalysts incorporating two internal basic moieties may find broad application in organocatalyzed Michael additions.

Keywords: asymmetric catalysis; C–C coupling; iminium ion activation; Michael addition; organocatalysis; α,β-unsaturated aldehydes

Introduction

The Michael addition to α,β-unsaturated systems is one of the fundamental bond-forming processes in organic chemistry and offers an extremely powerful tool for the synthesis of functionalized organic molecules.[1] Among the many nucleophiles that can be employed in this reaction nitroalkanes stand out as especially useful, as the resulting products can be converted to ketones, reduced to an amines, or modified by radical substitution with hydrogen.[2] With such a plethora of possibilities, it is not surprising that asymmetric implementations of this Michael addition have attracted much attention in the past decade. Various catalyst have been utilized for the asymmetric 1,4-addition of nitroalkanes to chalcones,[3] including a recently developed Al-salen complex[4] and a system based on nanocrystalline MgO.[5]

Asymmetric conjugate addition to enones has been developed to also include organocatalytic methodologies.[6] Organocatalytic methodologies often take advantage of the possibility for temporary covalent bonding of the catalyst to form an iminium cation which dramatically increases the reactivity towards nucleophiles due to lowered energy of the LUMO (lowest unoccupied molecular orbital) making bonding energetically more favorable.[7] Several organocatalytic systems (Figure 1) have been developed for conjugate additions of nitroalkanes to enones:

L-Proline rubidium salt,[8a,b] L-proline **1** in the presence of 2,5-dimethylpiperazine,[9] imidazoline catalyst **2**,[10] chiral diamine-dipeptide catalyst,[11] tetrazole-containing imidazoline catalyst **3**,[12] and the L-proline-derived tetrazole catalysts **4** and the homologous analogue **5** in the presence of 2,5-dimethylpiperazine.[13,14]

Despite these impressive developments of organocatalytic systems enabling addition of nitroalkanes to α,β-unsaturated ketones, the protocol for achieving the same type of reactions with the corresponding α,β-unsaturated aldehydes is far more embryonic. The major reason for the absence of representative examples relates to the fact that enals readily undergo 1,2-addition instead of the desired selective 1,4-addition. To the best of our knowledge, there are only a few examples of the catalytic asymmetric addition of nitroalkanes to an α,β-unsaturated aldehydes. The most suc-

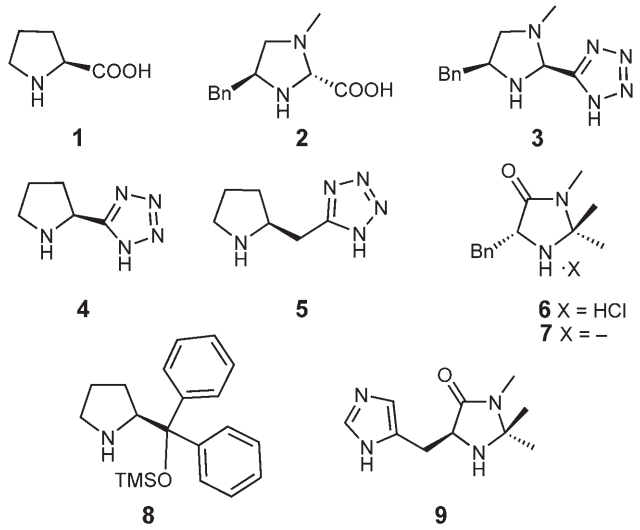


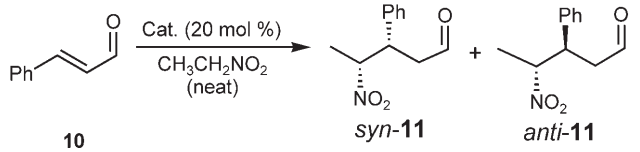
Figure 1. Organocatalysts discussed in the text.

cessful, in terms of yield and selectivity, is based on a chiral phase-transfer catalyst for the addition of silyl nitronates to aldehyde,[16] while two other papers report on the organocatalyzed conjugate addition of nitroalkanes to enals although only with limited success, 46% *ee* for addition to crotonaldehyde[13,14] and 29% *ee* for addition to hexenal.[8b] In this paper, we give a full account of our progress in the organocatalyzed enantioselective conjugate addition of nitroalkanes to enals utilizing a novel type of catalyst (**9**) closely resembling MacMillan's well known imidazolidinone catalyst (**6**). Structural modifications enabled a modulation of the reactivity, for example, allowing incorporation of enals as a reactive partner but at the same time retaining important features such as control of iminium ion geometry and existence of directing steric bulk.

Results and Discussion

Initially, the efficiency, e.g., reactivity and selectivity of the various organocatalysts previously described in the literature, for the Michael addition of nitroethane to *trans*-cinnamaldehyde **10** to yield 4-nitro-3-phenylpentanal (**11**) (Table 1) was investigated. The tetrazole analogue of proline **4** which has proven to readily facilitate the reactions between α,β-unsaturated ketones and nitroalkanes in the presence of 2,5-dimethylpiperazine,[13,14] turned out to be a less suitable catalyst for the addition to α,β-unsaturated aldehydes, proceeding only in moderate yield and with low enantioselectivity (Table 1, entry 1). Homologous tetrazole **5** provided the product in good yield and enantioselectivity (Table 1, entry 2), even in the absence of added base. No conversion was observed with the hydrochloric salt of the MacMillan organocatalyst **6**, or

Table 1. Initial investigation of various organocatalysts for the 1,4-addition of nitroethane to *trans*-cinnamaldehyde (**10**) to yield 4-nitro-3-phenylpentanal (**11**).[a]



Entry	Catalyst	Time [h]	Yield [%][b]	*syn*:*anti*[c]	*ee* [%][d]
1	**4**	150	60	1:1.2	33:30
2	**5**	48	82	1:1	66:73
3	**6**	72	0	-	-
4	**7**	100	0	-	-
5	**8**	15	91	1:1.2	49:5

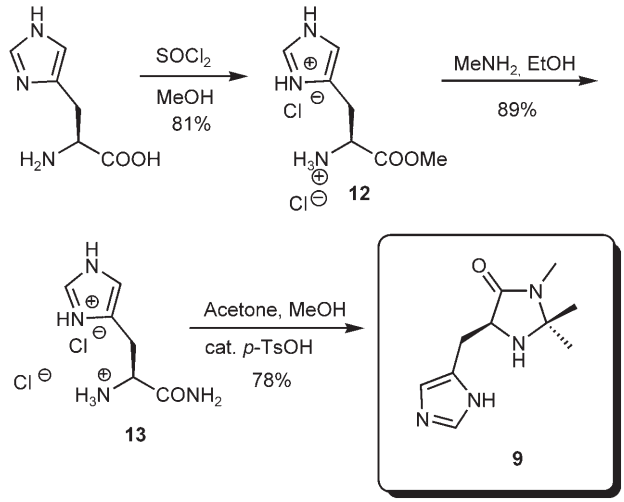
[a] **10** (0.5 mmol), catalyst (20 mol%), nitoethane (2 mmol).
[b] Isolated yield after column chromatography.
[c] Determined by ^{1}H NMR.
[d] Determined by GC-MS using a chiral column [Astec Chiradex X-TA].

with the neutral form of the catalyst, i.e., **7** (Table 1, entries 3 and 4). Finally, catalyst **8** was tested; this catalyst was found to be the most reactive, giving 91% conversion in only 15 h, but with moderate enantioselectivity for the *syn* diastereomer and a poor enantioselectivity for the *anti* adduct (Table 1, entry 5).

Based on these results, and on those reported in the literature for ketone substrates, we reasoned that it would be advantageous to build in a basic unit within the catalyst. The most straightforward catalyst, in terms of synthetic efficiency, we could think of was the novel imidazole containing the MacMillan type of catalyst **9** Although the imidazole ring of catalyst **9** is too weak a base (pK_a of conjugate acid approx. 7) to promote extensive deprotonation of the substrate ($pK_a \approx 9$) in water, the pK_a difference in an organic solvent like DMSO is on the other hand in favor of the catalyst deprotonating the substrate (pK_a of nitroalkanes approx. 17, pK_a of imidazole approx. 19).[15]

The new catalyst **9** was synthesized from L-histidine according to a procedure similar to that reported for synthesis of catalyst **6**.[7] The synthesis commenced with the preparation of the methyl ester of L-histidine which then was transformed into the corresponding methylamide·2 HCl salt. After filtration of the highly hydroscopic amide dihydrochloric salt under an inert atmosphere, it was directly cyclized to the corresponding imidazolidinone **9** through acid-catalyzed condensation with acetone generating a transient imine which upon protonation undergoes the desired cyclization (Scheme 1).

Catalyst **9** was evaluated under the same conditions as used for the other catalysts in Table 1. As seen in Table 2, this catalyst did indeed provide the product in high yield and enantioselectivity (Table 2, entry 1).



Scheme 1. Synthesis of (5*S*)-5-[(1*H*-imidazol-5-yl)methyl]-2,2,3-trimethylimidazolidin-4-one (**9**).

Table 2. Evaluation of the new imidazole based catalyst **9** (20 mol%) for the archetypical reaction between nitroethane and *trans*-cinnamaldehyde (**10**) (see Table 1) under various reaction conditions. No 1,2-addition was observed.

Entry	Solvent	Time [h]	Conversion [%][a]	*syn:anti*[a]	*ee* [%][b]
1[c]	-	47	93	1:1	82:80
2[d]	THF	48	22	1:1.2	72:68
3[d]	DMF	48	39	1:1	92:90
4[e]	DMF	70	79	1:1	90:86
5[f]	CH_2Cl_2	64	14	1:1.4	90:85
6[f,g]	CH_2Cl_2	64	35	1:1.2	81:76
7[d]	CH_3CN	48	22	1:1	50:46
8[d]	CH_3OH	48	44	1:1.2	65:60

[a] Determined by ^{1}H NMR.
[b] Determined by GC-MS using a chiral column [Astec Chiradex X-TA].
[c] **10** (0.5 mmol), $EtNO_2$ (2 mmol).
[d] **10** (0.1 mmol), $EtNO_2$ (0.4 mmol), solvent (0.2 mL).
[e] **10** (0.1 mmol), $EtNO_2$ (0.4 mmol), solvent (0.1 mL).
[f] **10** (0.25 mmol), $EtNO_2$ (1 mmol), solvent (1 mL).
[g] 0.25 equivs. H_2O added

Although the reaction is not as fast as that with catalyst **8** (Table 1, entry 5), the new catalyst produced the product in the same yield, and with the best selectivity of the catalysts evaluated. The effect of solvent was also investigated by performing the archetypical reaction between *trans*-cinnamaldehyde and nitroethane in various solvents with 20 mol-percent of catalyst (Table 2, entries 2–8).

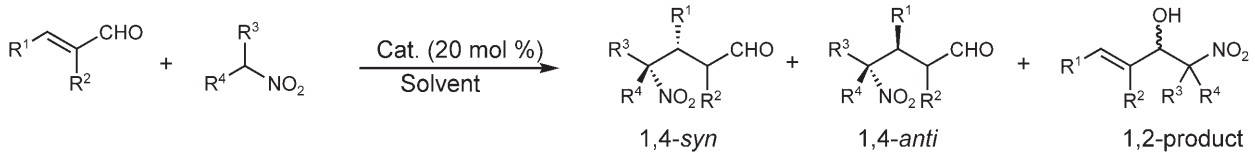
It is evident that the rate of reaction is reduced in the presence of additional solvent. Excellent enantioselectivity was obtained in DMF, but unfortunately the reaction was too slow to be practically useful (Table 2, entry 3). Increasing the concentration of reactants, while prolonging the reaction time resulted in higher conversion (Table 2, entry 4) while enantioselectivity was kept at acceptable levels. Addition of water was found to increase the rate of the reaction but concurrently decreasing enantioselectivity when dichloromethane was used as solvent (Table 2, entries 5 and 6). Poor conversion and moderate to acceptable enantioselectivities were obtained in THF, CH_3CN, and methanol (Table 2, entries 2, 7 and 8). Consequently, neat reaction condition appeared to offer the best compromise between reactivity and enantioselectivity. It should be noted that the initial reaction between *trans*-cinnamaldehyde (**10**) and nitroethane catalyzed by catalyst (**9**) indicated that no 1,2-addition was observed (*vide infra*).

After these initial experiments, the possibility of elaborating the nitroalkane structure was investigated. Nitromethane and 2-nitropropane were examined, especially since the bulkier 2-nitropropane was expected to yield an increased enantioselectivity in the product. Unfortunately, the results obtained employing nitromethane as donor displayed a non-selective reaction, propably due to a second consecutive nucleophilic attack by the 1,4-product towards the accessible α,β-unsaturated aldehyde, accompanied by low enantiocontrol (Table 3, entry 1). Reaction employing 2-nitropropane was sluggish only furnishing 65% isolated yield and 48% *ee* after a reaction time of 170 h (Table 3, entry 2)

Next, we investigated the scope for the aldehyde substrate. Surprisingly, when α-methyl-*trans*-cinnamaldehyde was utilized as a Michael acceptor, the separated product was not in accord with that expected. The NMR spectrum showed that significant 1,2-addition had taken place (Table 3, entry 3). Utilization of other organocatalysts to achieve the 1,4-Michael addition for this substrate was also unprofitable (data not shown). Most likely, the α-methyl group prevents the catalyst from forming the desired iminium ion thereby seriously reducing the reactivity; also catalysts **4** and **5**, which have a monosubstituted pyrrolidine ring, gave sluggish reactions rendering mostly 1,2-addition adduct.

Significant 1,2-addition was also observed with the electron-withdrawing nitro group on the phenyl ring in cinnamaldehyde; both the *ortho*- and *para*-nitrocinnamaldehydes yielded 1,2-addition products (Table 3, entries 4 and 5). The lack of solubility of the starting materials prohibited neat reaction conditions to be employed, thus making the use of solvent inevitable. Based on our results in Table 2, we considered DMF as the solvent of choice. It was predicted that the reactions involving nitrocinnamaldehyde would display an acceptable rate even in the presence of DMF as solvent. Our experiments showed formation of both unwanted 1,2-addition product and desired 1,4-addition product for both nitroethane and nitropropane, thus yielding a plurality of regioisomeric and diastereomeric products that were difficult to separate.

Table 3. Addition of nitroalkanes to α,β-unsaturated aldehydes catalyzed by **9**.



Entry	R^1	R^2	R^3	R^4	Solvent	Time	Yield [%][a]	1,2-:1,4-addition[b]	*syn*:*anti*[b]	*ee*[c] [%]
1[d]	Ph	H	H	H	-	72 h	36 [g]	0:1	-	47
2[d]	Ph	H	Me	Me	-	170 h	65 [g]	0:1	-	48
3[d]	Ph	Me	Me	H	-	4 d	20 [h]	1:0	-	-
4[e]	*p*-$NO_2C_6H_4$[f]	H	Et	H	DMF	2 d	62[i]	1:1.1	1.2:1	-
5[e]	*o*-$NO_2C_6H_4$	H	Et	H	DMF	2 d	48[i]	1.3:1	1.2:1	-
6[d]	*n*-Pr	H	Me	H	-	40 h	74 [g]	0:1	1:1	16:9

[a] Isolated yield after column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by GC-MS using a chiral column [Astec Chiradex X-TA].
[d] Aldehyde (0.5 mmol), nitroalkane (2 mmol).
[e] Aldehyde (0.5 mmol), nitroalkane (2 mmol), solvent (0.2 mL).
[f] Predominantly *trans*-
[g] Yield is related to 1,4-adduct.
[h] Yield is related to 1,2-adduct.
[i] Yield is related to the total of 1,2 and 1,4- adduct.

One aliphatic aldehyde was also investigated under neat reaction conditions (Table 3, entry 6). The reaction yielded exclusively the 1,4-adduct in fair yield but the enantioselectivity was poor only (16:9). Likewise, the ability of catalyst **9** to effect the 1,4-addition of nitroalkanes to ketones was investigated by employed 2-cyclohexenone as a substrate in neat nitromethane. Despite prolonged reaction time, no product was observed in this case, probably due to steric repulsion of two methyl groups on the imidazolidinone ring on catalyst **9**. Overall, these results (Table 3, entries 1–6) suggest that aliphatic aldehydes and α,β-unsaturated ketones are not good substrates under the present reaction conditions. A non-substituted analogue of this catalyst is thus expected to be required in order to provide good conversions for ketone substrates.

A series of different enals was employed as Michael acceptors for two different straight-chain nitroalkanes as shown in Table 4. Due to the lower reactivity of nitropropane, a longer reaction time was needed for reaction compared to nitroethane (*cf.* entries 1 and 2). Although both the reaction rate and enantioselectivity were decreased when the smaller and more electrophilic furyl group was used instead of a phenyl group (*cf.* entries 1 and 3), both acceptable relative and specific stereochemistry could be obtained (Table 4 entries 3 and 4). An electron-donating methoxy group in the *ortho*-position on the phenyl ring increased the reaction rate and both diastereoselectivty and enantioselectivty (entries 5 and 6). As seen in Table 4 entry 6, this substrate yieled an excellent stereoselectivity (up to 90%) for the nitropropane adduct. The positive effect of *o*-OMe is counterbalanced on changing the substitution pattern to *p*-OMe as seen in Table 4 (entries 7 and 8); however the diastereoselectivities and enantioselectivities obtained were still fair.

Conclusions

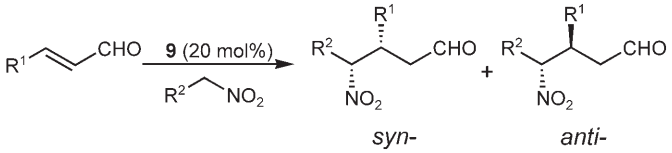
In conclusion, we have disclosed an organocatalytic, enantioselective Michael addition of nitroalkanes to α,β-unsaturated aldehydes using a new imidazole-based catalyst. The catalyst readily facilitates reactions between straight-chain nitroalkanes and non-α-substituted aromatic α,β-unsaturated aldehydes providing access to β,γ-functionalized saturated aldehydes in isolated yields of up to 91% and enantioselectivities of up to 92%. Although the results indicate a limited substrate scope, in terms of permitted nitroalkanes and α,β-unsaturated aldehydes, they are still the best obtained for the organocatalyzed Michael addition of nitroalkanes to enal substrates, and provide proof of principle that organocatalysts with an internal basic moiety are indeed advantageous for this reaction.

Experimental Section

General Remarks

Chemicals and solvents were either purchased *puris p.A.* from commercial suppliers or purified by standard techniques. For thin layer chromatography (TLC), precoated

Table 4. Catalytic asymmetric organocatalyzed Michael addition of nitroethane and nitropropane to α,β-unsaturated aldehydes employing organocatalyst **9**.[a]



Entry	R^1	R^2	Time [h]	Yield [%][b]	*syn*:*anti*[c]	ee[d] [%]
1	Ph	Me	47	91	1:1	82:80
2	Ph	Et	68	75	1:1	74:63
3	2-Furyl	Me	68	61	1:1.1	68:66
4	2-Furyl	Et	48	49	1:1	77:67
5	*o*-MeO-C_6H_4[e]	Me	45	91	1:2.3	68:71
6	*o*-MeO-C_6H_4[e]	Et	49	81	1:2.6	90:79
7	*p*-MeO-C_6H_4	Me	65	60	1:1.3	77:56
8	*p*-MeO-C_6H_4	Et	62	43	1:1.3	68:53

[a] Unsaturated aldehyde (0.5 mmol), nitroalkane (2 mmol).
[b] Isolated product after column chromatography.
[c] Determined by ^{1}H NMR.
[d] Determined by GC-MS using a chiral column [Astec Chiradex X-TA] or HPLC using a Daicel Chiralcel AS-H column.
[e] Predominantly *trans*.

0.25 mm silica plates (Macherey–Nagel 60 Alugram® Sil G/UV_{254}) were used and spots were visualized either with UV light or by heating after soaking the TLC plate in a solution consisting of 0.5% 2,4-dinitrophenylhydrazine in 2 M HCl. Column chromatography was performed on silica gel (Matrex™ 60 A, 37–70 μm) and basic alumina oxide supplied by ICN EcoCHROM. ^{1}H NMR (500 and 300 MHz) spectra were recorded on Varian Unity 500 MHz and Varian Mercury plus 300 MHz spectrometer, respectively, and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Mercury plus 300 MHz spectrometer. All spectra were acquired at ambient temperature. Chemical shifts (δ) in ppm are reported using residual chloroform or methanol as internal reference (^{1}H $\delta = 7.26$, ^{13}C $= \delta$ 77.0) or (^{1}H $\delta = 3.30$, ^{13}C $\delta = 49.0$) and coupling constants (*J*) are given in Hz. Infrared spectra was recorded on a Perkin–Elmer Spectrum 100 FT/IR spectrometer. Melting point determination was done using a SMP3 melting point apparatus supplied by Stuart Scientific and are uncorrelated. Purity of catalyst was confirmed by elemental analysis performed by Mikro Kemi Uppsala and by means of a high pressure liquid chromatography (HPLC) system coupled to an MS detector and an evaporative light-scattering detector (ELSD); the system consisted of a Gilson 322 pump, Gilson 233 XL autosampler and a Gilson UV/VIS 152 detector, coupled in series with a Finnigan AQA mass spectrometer and an ELSD (Sedex 85 CC) from Sedere. The reverse phase HPLC analysis was done using a Phenomenex Gemini C18 (3 μ, 3.0×150 mm) column employing acetonitrile-water (both containing 0.1% formic acid) as mobile phase (gradient: 5–95% acetonitrile in 6 min + 6 min at 95%, flow 1.0 mL min^{-1}). Enantiomeric excesses were determined using a high pressure liquid chromatography (HPLC) system equipped with a column consisting of a chiral stationary phase (4 μm, 0.46×250 mm) supplied by Daicel Chemical Industries, Ltd. The HPLC system consisted of a Gilson 322 pump, Gilson 233 XL autosampler, and an Agilent 1100 diode-array detector. Details concerning mobile phase compositions and column types are presented below individually for each compound. GC-MS determination of enantiomeric excesses was done using a Varian CP-8410 auto injector and a Varian Saturn 2100T GC-MS system equipped with a column (30 m×0.25 mm), consisting of fused silica capillary tubing coated with a chiral stationary phase (film thickness 0.125 μm) supplied by Astec with helium gas at 10 psi as carrier gas. Details concerning the columns and temperature programs used are given specifically for each compound below.

Methyl (2*S*)-2-Amino-3-(1*H*-imidazol-4-yl)propanoate Dihydrochloride (13)

To a stirred solution of L-histidine (3.87 g, 24 mmol) in dry methanol (50 mL) kept at 0 °C was added thionyl chloride (2.72 mL, 37.5 mmol). After 15 min at 0 °C, the reaction mixture was allowed to warm to room temperature, and then refluxed for 48 h. The solution was concentrated under vacuum and L-histidine methyl ester dichloride crystallized from methanol to give white crystals; yield: 4.7 g (81%). ^{1}H NMR and ^{13}C NMR are identical with commercially available material.

(2*S*)-2-Amino-3-(1*H*-imidazol-4-yl)-*N*-methylpropanamide (12)

To a solution of ethanolic $MeNH_2$ (8 M, 6 mL) was added L-histidine methyl ester dihydrochloride **13** (2.41 g, 10 mmol). The solution was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and CH_2Cl_2 (20 mL), Na_2CO_3 (7 g) and H_2O (2 mL) were added and the resulting mixture was stirred for 1 hour before filtration of the resulting precipitate. Boiling *i*-PrOH was added to the solid under a stream of N_2 before the solid was filtered under an inert atmosphere. The *i*-PrOH was removed under reduced pressure to give a white powder; yield: 2.14 g

(89%). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 2.6$ (s, 3H), 2.9–3.10 (dd, $J = 14$, 4.9 Hz, 2H), 3.9 (dd, $J = 8.3$, 4.9 Hz, 1H), 6.9 (s, 1H), 7.6 (s,1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 28$, 34, 52, 120, 132, 137, 172.

(5*S*)-5-[(1*H*-Imidazol-5-yl)methyl]-2,2,3-trimethyl-imidazolidin-4-one (9)

To (2*S*)-2-amino-3-(1*H*-imidazol-4-yl)-*N*-methylpropanamide (3.64 g, 15.2 mmol) was added 30 mL dry MeOH, acetone (5.8 mL, 4.59 g; 79 mmol) and a catalytic amount of *p*-toluenesulfonic acid (30 mg, 0.16 mmol). The resulting solution was refluxed for 24 h and stirred at room temperature for 2 h. The mixture was subsequently concentrated under reduced pressure giving the crude product as a yellow oil. The crude product was purified by means of column chromatography using basic alumina oxide and CH_2Cl_2:MeOH (9:1; $R_f = 0.54$) to give a slightly red colored oil; yield: 2.46 g (78%). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 1.28$ (d, $J =$ 2.1 Hz, 6H), 2.75 (d, $J = 0.74$ Hz, 3H), 2.85–2.95 (ddd, $J =$ 15, 7.3, 0.75 Hz, 1H), 3.0–3.10 (ddd, $J = 15$, 4.3, 0.85 Hz, 1H), 3.76–3.8 (ddd, $J = 7.3$, 4.3, 0.73 Hz, 1H) 6.9 (s, 1H), 7.59 (d, $J = 1.23$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD): $\delta =$ 24.9, 25.5, 27.0, 29.6, 59.7, 77.5, 118.7, 136.2, 175.3.

In order to provide a crystalline material, 2.46 g of the free base were dissolved in approximately 30 mL dry methanol. To the mixture was then added hydrogen chloride in ether. Under vigorous stirring was added dry diethyl ether until formation of a precipitate was visible. The precipitate was filtered under N_2 and recrystallized from a mixture of 2-propanol and methanol to furnish **9**·2HCl salt as white flakes; yield: 2.52 g (76%); mp 225–227 °C. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 1.65$ (s, 3H), 1.81 (s, 3H), 2.91 (d, $J = 0.6$ Hz, 3H), 3.40–3.46 (ddd, $J = 15.83$, 8.53, 0.8 Hz, 1H), 3.49–3.55 (ddd, $J = 15.85$, 5.97, 0.97 Hz, 1H), 4.62–4.66 (ddd, $J = 8.53$ 5.97 0.80 Hz, 1H), 7.6 (s, 1H), 8.9 (d, $J = 1.39$ Hz, 1H); ^{13}CNMR (75 MHz, CD_3OD): $\delta = 23.6$, 25.6, 25.9, 26.6, 57.4, 80.2, 120.4, 130.1, 136.4, 168; IR (neat): $\nu = 3119$, 2571, 2326, 1718, 1573, 1384, 1065, 783, 676 cm^{-1}; HPLC-MS: $R_t =$ 0.9 min; MS (ESI): $m/z = 211$ $[M+3H]^+$; $[\alpha]_D^{25}$: −36° (*c* 1.00, MeOH) measured on crystalline **9**·2HCl; anal. calcd. for $C_{10}H_{18}Cl_2N_4O$: C 42.7, H 6.45, N 19.9; found: C 42.4, H 6.4, N 19.6.

General Procedure for the Catalytic Asymetric Michael Addition of Nitroalkane to α,β-Unsaturated Aldehydes

To 0.1 mmol of the catalyst in a flask equipped with a magnetic stirring bar was added 0.5 mmol of the α,β-unsaturated aldehyde and 2 mmol of the nitroalkane (and in those cases indicated a solvent). The reaction mixture was stirred at room temperature using N_2 as protecting atmosphere, individual reaction times are given in the respective tables. Reaction progress was monitored by thin layer chromatography and spots were visualized using UV light or by heating after soaking the TLC plates in a solution of 0.5% 2,4-dinitrophenylhydrazine in 2M HCl. The crude reaction mixture was concentrated under reduced pressure in order to remove nitroalkane after which the residue was purified by means of column chromatography using silica gel and either (pentane:ethyl acetate) (9:1) or (pentane:diethyl ether) (80:20).

4-Nitro-3-phenylpentanal (Table 1)

Syn: Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (d, $J = 6.9$ Hz, 3H), 2.71–3.02 (m, 2H, CH_2C=O), 3.71–3.79 (dt, $J = 9.9$, 4.5 Hz, 1H), 4.73–4.83 (m, 1H), 7.20 (m, 2H), 7.29–7.39 (m, 3H), 9.56 (dd, $J = 2.1$, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.7$, 44.2, 46.4, 87.1, 128.1, 128.2, 129,2, 137.5, 198.6. The enantiomeric excess was determined by means of GC-MS using an Astec Chiradex X-TA column, 150 °C isothermal, $t_r = 19.3$ min (major) and 22.5 min (minor). MS (EI): *m/z* (rel. intensity) = 160 (1), 143 (50), 131 (25), 117 (50), 105 (55), 91 (100),

Anti: The enantiomer of this compound has been characterized previously.[16] The enantiomeric excess was determined using an Astec Chiradex X-TA column, 150 °C isothermal, $t_r = 21.5$ min (minor) and 23.9 min (major). MS (EI): *m/z* (rel. intensity) = 160 (100), 143 (25), 131 (30), 117 (50), 105 (40), 91 (80), 65 (27).

4-Methyl-4-nitro-3-phenylpentanal (Table 3, entry 2)

Colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.48$ (s, 3H), 1.57 (s, 3H), 2.67–3.11 (m, 2H), 3.99 (dd, $J = 11.2$, 3.7 Hz, 1H), 7.18–7.22 (m, 2H), 7.28–7.33 (m, 3H), 9.52 (dd, $J = 2.4$, 0.6 Hz, 1H); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 22.2$, 25.5, 43.9, 47.6, 91.0, 128.1, 128.7, 129.2, 136.8, 199.0. The enantiomeric excess was determined using an Astec Chiradex X-TA column, 140 °C isothermal, $t_r = 40.7$ min (minor) and 42.1 min (major). MS (EI): *m/z* (rel. intensity) = 220 (M^+, 10), 191 (25), 174 (30), 157 (30), 145 (60), 131 (100), 117 (30), 91 (25).

4-Nitro-3-(4-nitrophenyl)hexanal (Table 3, entry 4)

Syn: Slightly yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.88 (t, $J = 7.5$ Hz, 3H), 1.40–1.54 (m, 1H), 1.78–1.93 (m, 1H), 2.82–3.11 (m, 2H, CH_2C=O), 3.85–3.93 (dt, $J = 9.9$, 3.6 Hz, 1H), 4.60–4.68 (dt, $J = 10.3$, 3.3 Hz, 1H), 7.42 (d, $J =$ 9 Hz, 2H), 8.22 (d, $J = 9$ Hz, 2H), 9.59 (d, $J = 0.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.2$, 25.5, 42.8, 46.2, 93.1, 124.4, 129.2, 145.6, 147.6, 197.4

Anti: Slightly yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.99 (t, $J = 7.2$ Hz, 3H), 1.78–2.04 (m, 2H), 2.92–3.14 (m, 2H, CH_2C=O), 3.88–3.95 (m, 1H), 4.70–4.78 (ddd, $J = 10.3$, 7.8, 3.9 Hz, 1H), 7.37 (d, $J = 9$ Hz, 2H), 8.18 (d, $J = 9$ Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.3$, 24.8, 42.2, 45.4, 92.7, 124.0, 129.2, 145.2, 147.6, 197.7.

4-Nitro-3-(2-nitrophenyl)hexanal (Table 3, entry 5)

Syn: Slightly yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.94 (t, $J = 7.5$ Hz, 3H), 1.56–1.68 (m, 1H), 2.00–2.15 (m, 1H), 2.94–3.12 (m, 2H, CH_2C=O), 4.37–4.44 (ddd, $J = 9.3$, 8.1, 4.5 Hz, 1H), 4.79–4.87 (ddd, $J = 10.8$, 8.1, 3.6 Hz, 1H), 7.29 (dd, $J = 7.7$, 1.2, Hz, 1H), 7.45 (dt, $J = 8.1$, 1.2 Hz, 1H), 7.59 (dt, $J = 7.7$, 1.2 Hz, 1H), 7.89 (dd, $J = 8.1$, 1.2 Hz, 1H), 9.58 (d, $J = 0.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 10.4, 25.5, 36.8, 45.3, 93.4, 125.2, 128.5, 128.8, 133.0, 133.3, 150.1, 197.8.

Anti: Slightly yellow oil, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.98 (t, $J = 7.5$ Hz, 3H), 1.86–1.97 (m, 2H), 2.90–3.19 (m, 2H, $CH_2C{=}O$), 4.44–4.52 (m, 1H), 4.94–5.02 (dt, $J = 9$, 4.5 Hz, 1H), 7.41–7.46 (m, 2H), 7.58 (dt, $J = 7.8$, 1.2 Hz, 1H), 7.85 (dd, $J = 8.2$, 1.2 Hz, 1H), 9.58 (t, $J = 1.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.2$, 24.8, 37.3, 45.5, 92.1, 125.2, 129.0, 129.4, 132.5, 133.2, 150.1, 198.3.

3-(1-Nitroethyl)hexanal (Table 3, entry 6).

The enantiomer of this compound has been characterized previously.[16] Both *syn* and *anti:* MS (EI): *m/z* (rel. intensity) = 174 (2), 144 (5), 127 (8), 109 (20), 83 (60), 67 (20), 55 (100), 41 (30).

4-Nitro-3-phenylhexanal (Table 4, entry 2)

Syn: White crystals, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.5$ Hz, 3H), 1.43–1.56 (m, 1H), 1.75–1.91 (m, 1H), 2.66–3.01 (m, 2H, $CH_2C{=}O$), 3.69–3.77 (dt, $J = 10.3$, 3.9 Hz, 1H), 4.56–4.64 (dt, $J = 10.5$, 3.3 Hz, 1H), 7.19–7.22 (m, 2H), 7.28–7.35 (m, 3H), 9.54 (dd, $J = 2.1$, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.2$, 25.4, 43.5, 46.5, 94.2, 128.1, 128.1, 129.3, 137.9, 198.6. The enantiomeric excess was determined using an Astec Chiradex X-TA column, 160 °C isothermal, $t_r = 12.8$ min (major) and 13.6 min (minor).

Anti: The enantiomer of this compound has been characterized previously.[16] The enantiomeric excess was determined using an Astec Chiradex X-TA column, 160 °C isothermal, $t_r = 14.2$ min (minor) and 14.9 min (major). MS (EI): *m/z* (rel. intensity) = 191 (5), 174 (80), 145 (20), 131 (100), 105 (75), 91 (80), 77 (30), 51 (25).

3-(Furan-2-yl)-4-nitropentanal (Table 4, entry 3)

Syn: White crystals, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (d, $J = 6.9$ Hz, 3H), 2.67–3.04 (m, 2H, $CH_2C{=}O$), 3.94–4.02 (dt, $J = 9.6$, 4.5 Hz, 1H), 4.76–4.87 (m, 1H), 6.22 (d, $J =$ 3 Hz, 1H), 6.32 (dd, $J = 3$, 1.8 Hz, 1H), 7.36 (d, $J = 1.8$ Hz, 1H), 9.65 (dd, $J = 1.8$, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.1$, 37.5, 43.8, 84.9, 109.0, 110.6, 142.7, 150.2, 198.2. The enantiomeric excess was determined using an Astec Chiradex X-TA column, 150 °C isothermal, $t_r = 8.5$ (major) min and 9.4 min(minor). MS (EI): *m/z* (rel. intensity) = 167 (8), 150 (100), 122 (80), 107 (50), 95 (40), 79 (50), 67 (30), 55 (20).

Anti: White crystals, ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.52$ (d, $J = 6.6$ Hz, 3H), 2.95 (dd, $J = 7.2$, 1.2 Hz, 2H, $CH_2C{=}O$), 3.97–4.03 (m, 1H), 4.85–4.94 (m, 1H), 6.16 (d, $J = 3.3$ Hz, 1H), 6.31 (dd, $J = 3.3$, 1.8 Hz, 1H), 7.35 (d, $J = 1.8$ Hz, 1H), 9.73 (t, $J = 1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.9$, 37.0, 42.5, 84.1, 108.3, 110.5, 142.6, 150.7, 198.6. The enantiomeric excess was determined using an Astec Chiradex X-TA column, 150 °C isothermal, $t_r = 9.9$ min (minor) and 11.1 min-(major). MS (EI): *m/z* (rel. intensity) = 198 (8), 167 (5), 150 (100), 122 (80), 107 (50), 95 (45), 79 (60), 67 (50), 55 (50), 41 (20).

3-(Furan-2-yl)-4-nitrohexanal (Table 4, entry 4)

Syn: White crystals, ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (t, $J =$ 7.5 Hz, 3H), 1.54–1.66 (m, 1H), 1.80–1.96 (m, 1H), 2.62–3.03 (m, 2H, $CH_2C{=}O$), 3.87–3.95 (dt, $J = 9.6$, 3.9 Hz, 1H), 4.63–4.71 (dt, $J = 7.7$, 3.6 Hz, 1H), 6.22 (dd, $J = 3.3$, 0.3 Hz, 1H), 6.31 (dd, $J = 3.3$, 1.8 Hz, 1H), 7.36 (dd, $J = 1.8$, 0.9 Hz, 1H), 9.62 (dd, $J = 1.6$, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.1$, 25.3, 36.8, 43.9, 91.9, 108.9, 110.6, 142.6, 150.5, 198.2. The enantiomeric excess was determined using an Astec Chiradex X-TA column, 150 °C isothermal, $t_r =$ 8.9 min (major) and 9.6 min (minor). MS (EI): *m/z* (rel. intensity) = 181 (10), 164 (80), 150 (100), 122 (80), 107 (50), 95 (45), 79 (60), 67 (50), 55 (50), 41 (20).

Anti: White crystals, ^{1}H NMR ($CDCl_3$): $\delta = 0.97$ (t, $J =$ 7.5 Hz, 3H), 1.72–1.86 (m, 1H), 1.93–2.09 (m, 1H), 2.94–2.98 (m, 2H, $CH_2C{=}O$), 3.94 (m, 1H), 4.67–4.74 (ddd, $J =$ 10.2, 6.2, 3.9 Hz, 1H), 6.15 (td, $J = 3.3$, 0.6 Hz, 1H), 6.30 (dd, $J = 3.3$, 1.8 Hz, 1H), 7.35 (dd, $J = 1.8$, 0.9 Hz, 1H), 9.72 (t, $J = 1.2$ Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 10.4$, 23.9, 36.3, 43.0, 91.3, 108.3, 110.5, 142.6, 150.8, 198.6. The enantiomeric excess was determined using an Astec Chiradex X-TA column, 150 °C isothermal, $t_r = 10.1$ min (minor) and 11.7 min (major). MS (EI): *m/z* (rel. intensity) = 181 (5), 164 (75), 149 (30), 121 (100), 108 (75), 95 (70), 77 (75), 67 (80), 55 (60), 41 (45).

3-(2-Methoxyphenyl)-4-nitropentanal (Table 4, entry 5)

Syn: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 1.33$ (d, $J =$ 6.9 Hz, 3H), 2.65–2.72 (m, 1H, $CH_2C{=}O$), 3.02–3.12 (m, 1H, $CH_2C{=}O$), 3.86 (s, 3H), 3.96–4.04 (dt, $J = 9.9$, 4.2 Hz, 1H), 5.02–5.12 (m, 1H), 6.87–6.96 (m, 2H), 7.17 (dd, $J = 7.5$, 1.8 Hz, 1H), 7.25 (ddd, $J = 8.1$, 7.5, 1.8 Hz, 1H), 9.54 (dd, $J = 2.1$, 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.3$, 40.7, 44.9, 55.3, 85.9, 111.1, 121.1, 125.5, 129.3, 130.4, 157.1, 199.6. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 5:95 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r = 26.8$ min (minor) and 28.5 min (major).

Anti: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 1.50$ (d, $J = 6.6$ Hz, 3H), 2.84–3.04 (m, 2H, $CH_2C{=}O$), 3.86 (s, 3H), 4.13–4.20 (m, 1H), 5.03–5.13 (m, 1H), 6.87–6–92 (m, 2H), 7.06 (dd, $J = 7.7$, 1.2 Hz, 1H), 7.26 (m, 1H), 9.63 (dd, $J = 2.2$, 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.5$, 39.0, 43.4, 55.4, 84.6, 111.1, 120.9, 125.4, 129.2, 129.5 157.1, 199.9. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 5:95 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r = 40.3$ min (major) and 43.7 min (minor).

3-(2-Methoxyphenyl)-4-nitrohexanal (Table 4, entry 6)

Syn: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 0.85$ (t, $J =$ 7.5 Hz, 3H), 1.42–1.54 (m, 1H), 1.74–1.90 (m, 1H), 2.60–3.11 (m, 2H, $CH_2C{=}O$), 3.86 (s, 3H), 3.99–4.07 (dt, $J = 10.2$, 4.2 Hz, 1H), 4.85–4.93 (dt, $J = 10.2$, 3.3 Hz, 1H), 6.87–6.95 (m, 2H), 7.16 (dd, $J = 7.5$, 1.8 Hz, 1H), 7.27 (ddd, $J = 8.1$, 7.5, 1.8 Hz, 1H), 9.54 (dd, $J = 2.2$, 1.1 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 10.2$, 25.6, 39.6, 44.9, 55.4, 92.8, 111.2, 121.1, 125.6, 129.3, 130.2, 157.1, 199.6. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 5:95 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r = 19.9$ min (minor) and 24.2 min (major).

Anti: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 0.96$ (t, $J =$ 7.5 Hz, 3H), 1.75–2.02 (m, 2H), 2.86–3.03 (m, 2H, CH_2C=O), 3.86 (s, 3H), 4.08 (m, 1H), 4.88–4.95 (ddd, $J = 10.6$, 8.2, 3.9 Hz, 1H), 6.86–6.91 (m, 2H), 7.06 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.25 (dt, $J = 7.8$, 1.5 Hz, 1H), 9.56 (t, $J = 1.5$ Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 10.5$, 24.4, 38.8, 44.1, 55.4, 91.9, 111.1, 120.9, 125.6, 129.2, 129.8, 157.1, 199.9. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 5:95 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r = 27.4$ min (major) and 33.2 min (minor).

3-(4-Methoxyphenyl)-4-nitropentanal (Table 4, entry 7)

Syn: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (d, $J =$ 6.6 Hz, 3H), 2.68–2.97 (m, 2H, CH_2C=O), 3.67–3.75 (dt, $J =$ 9.9, 4.5 Hz, 1H), 3.79 (s, 3H), 4.68–4.77 (m, 1H), 6.87 (d, $J = 8.7$ Hz, 2H), 7.11 (d, $J = 8.7$ Hz, 2H), 9.56 (dd, $J = 1.9$, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.6$, 43.5, 46.4, 55.3, 87.2, 114.6, 129.2, 129.2, 159.3, 198.8. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 20:80 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r = 20.3$ min (minor) and 27.3 min (major).

Anti: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 1.51$ (d, $J = 6.6$ Hz, 3H), 2.84–3.02 (m, 2H, CH_2C=O), 3.72–3.79 (m, 1H), 3.77 (s, 3H), 4.77–4.86 (m, 1H), 6.84 (d, $J = 8.7$ Hz, 2H), 7.09 (d, $J = 8.7$ Hz, 2H), 9.66 (t, $J = 1.3$ Hz, 1H); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 16.6$, 42.9, 44.9, 55.2, 86.5, 114.3, 129.1, 129.2, 159.3, 199.3. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 15:85 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r =$ 35.8 min (minor) and 39.5 min (major).

3-(4-Methoxyphenyl)-4-nitrohexanal (Table 4, entry 8)

Syn: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 0.85$ (t, $J =$ 7.5 Hz, 3H), 1.43–1.58 (m, 1H), 1.73–1.87 (m, 1H), 2.63–2.96 (m, 2H, CH_2C=O), 3.64–3.72 (dt, $J = 10.2$, 3.9 Hz, 1H), 3.79 (s, 3H), 4.50–4.59 (dt, $J = 10.5$, 3.3 Hz, 1H), 6.87 (d, $J =$ 8.7 Hz, 2H), 7.12 (d, $J = 8.7$ Hz, 2H), 9.53 (dd, $J = 2.1$, 0.9 Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 10.2$, 25.4, 42.8, 46.5, 55.3, 94.4, 114.7, 129.1, 129.6, 159.3, 198.9. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 5:95 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r = 36.7$ min (minor) and 45.0 min (major).

Anti: Slightly yellow oil, ^{1}H NMR ($CDCl_3$): $\delta = 0.97$ (t, $J =$ 7.5 Hz, 3H), 1.73–1.87 (m, 1H), 1.87–2.00 (m, 1H), 2.81–3.02 (m, 2H, CH_2C=O), 3.69–3.82 (m, 1H), 3.77 (s, 3H), 4.61–4.68 (ddd, $J = 10.5$, 7.2, 3.3 Hz, 1H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H), 9.64 (t, $J = 1.2$ Hz, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): $\delta = 10.4$, 24.5, 42.1, 45.5, 55.2, 93.7, 114.3, 129.1, 129.5, 159.3, 199.3. The enantiomeric excess was determined using HPLC with a Daicel Chiralpak AS-H column, 5:95 *i*-PrOH/hexane, 1 mL min^{-1} flow rate, $t_r = 46.7$ (minor) min and 49.2 min (major).

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