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Enantioselective Organocatalytic Michael Additions of Oxyacetaldehydes to Nitroolefins

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Alkyl and aryloxyacetaldehydes add enantioselectively to various nitroalkenes. Addition products were isolated in good yield and high enantiomeric purity (up to 96 % *ee*) but only mediocre *syn*/*anti* ratios were achieved. The course of the reaction was investigated by mass spectrometry and by DFT calculations.

Introduction

Michael addition is one of the most important C–C bond-forming reactions. A broad variety of stabilized as well as nonstabilized nucleophiles can add to numerous Michael acceptors, thus producing countless possibilities for the construction of interesting structures or building blocks suitable for further synthetic elaboration. Apart from a range of metal-based catalysts, a diverse array of small molecular weight organocatalysts has been investigated for Michael additions.[1] Both major concepts developed in organocatalysis and enamine[2] and iminium activation[3] can operate in conjugate addition. Carbonyl compounds can be rendered nucleophilic through enamine formation, and α,β-unsaturated carbonyl compounds can be activated through iminium formation. Furthermore, enantioselective 1,4-addition is not restricted to α,β-unsaturated carbonyl compounds. Nitroalkenes, alkenylphosphonates, and sulfones are also useful Michael acceptors.[4] In particular, nitroalkenes attract a lot of attention. After the seminal paper by List,[5] a number of organocatalyzed conjugate additions of simple ketones[6] and aldehydes to nitroolefins have been described.

Conjugate addition of aldehydes is more challenging due to the greater reactivity of the aldehyde functionality, which results in the undesired auto-aldol reaction. Several research groups successfully overcame this problem, and 1,4-additions of aldehydes have also been described recently. The first report on the enantioselective addition of simple aldehydes to nitroalkene was published by Barbas and later extended with good results also to α,α-disubstituted aldehydes.[7] Alexakis used a diamine catalyst that provided the addition product with high enantio- and diastereoselectivity.[8] Hayashi showed that diphenylprolinol silyl ethers catalyzed the addition of simple aldehydes to nitroalkenes with high diastereo- and enantioselectivities.[9] Lu and Chan achieved excellent results in this reaction with a modified diphenylperhydroindol silyl ether catalyst.[10] Replacement of the phenyl groups with 1-methylimidazole in prolinol silyl ether enabled the reaction to be performed in water.[11] Palomo used 4-hydroxyprolylamides as catalysts and obtained addition products with high diastereo- and enantioselectivities.[12] Other organocatalysts such as bimorpholine derivatives, tripeptides, and spirocyclic diamines have catalyzed this reaction as well.[13] Chiral thioureas were also shown to be viable catalysts for the addition of simple aldehydes to nitroalkenes.[14] Enantioselective addition of aldehydes to β-nitroacrolein dimethyl acetal was published by Vicario.[15] The best results (up to 88 %*ee*) were achieved with simple prolinol as the catalyst. The addition of benzyloxyacetaldehyde wasalso mentioned in this work, although for this particular example, the enantioselectivity was not reported because of HPLC detection problems. Later, Vicario and Badia expanded this methodology by applying enantioselective addition of aldehydes to nitroacrolein dimethylacetal in the construction of substituted pyrrolidines.[16] Alexakis described nitrodienes as acceptors in the addition of aldehydes and only 1,4-addition products have been obtained in high yields and with high enantioselectivities.[17]

Michael addition of acetaldehyde, as the most reactive enolizable aldehyde, constitutes a special challenge. List solved this issue by slow addition of acetaldehyde to the nitroolefin and thus obtained good yields and enantioselectivities.[18] On the other hand, functionalized acetalde-

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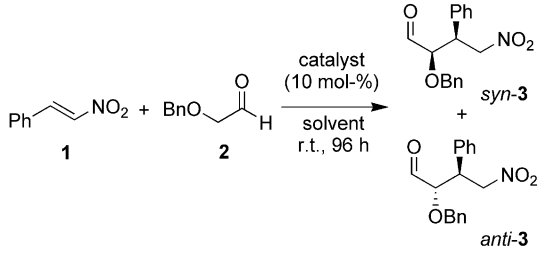
hydes are rather unreactive and their use as donors in organocatalyzed additions is rare. However, they represent valuable building blocks for target-oriented synthesis. MacMillan described the auto-aldol reaction of oxyaldehydes for the synthesis of carbohydrates.[19] Cordova used benzyloxyacetaldehyde in the Mannich reaction for the synthesis of the side chain of Paclitaxel.[20] Recently, Hayashi successfully utilized conjugate addition of 3-pentyloxyacetaldehyde to nitroacrylate en route to Oseltamivir.[21] These examples show the usefulness of oxyacetaldehydes in synthesis. Therefore, we decided to study the Michael addition of substituted oxyacetaldehydes. In this paper, we report the development of the enantioselective addition of oxyacetaldehydes to nitroalkenes.

Results and Discussion

Initial testing was performed with β-nitrostyrene (**1**) and benzyloxyacetaldehyde (**2**). However, no product was detected with the Jørgensen–Hayashi catalyst (**C1**)[9,22] in toluene (Scheme 1). The reactivity did not improve with use of an excess amount of aldehyde. On the other hand, if 5 equiv. of β-nitrostyrene was used, product **3** was isolated in good yield (86%), although as an inseparable mixture of *syn* and *anti* isomers. The diastereoselectivity of the reaction was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. To facilitate determination of the enantiomeric purity of product **3** by HPLC analysis, we reduced the aldehyde to the corresponding alcohol with $NaBH_4$.



Scheme 1.

To improve the addition of aldehyde **2** to β-nitrostyrene (**1**), we screened a series of common organocatalysts capable of enamine formation and thus benzyloxyacetaldehyde activation (Figure 1). This testing revealed that the Jørgensen–Hayashi catalyst (**C1**) was the most active one, and it afforded product **3** with the highest chemical yield (86%) and enantioselectivities (95 and 93% *ee*). With all organocatalysts except proline (**C9**), compound **3** was isolated with ca. 1:1 *dr*. (*S*)-Proline provided product **3** with better diastereoselectivity (*syn*/*anti*, 83:17), but the chemical yield and enantioselectivity were lower. The results of the catalyst screening are given in Table 1.

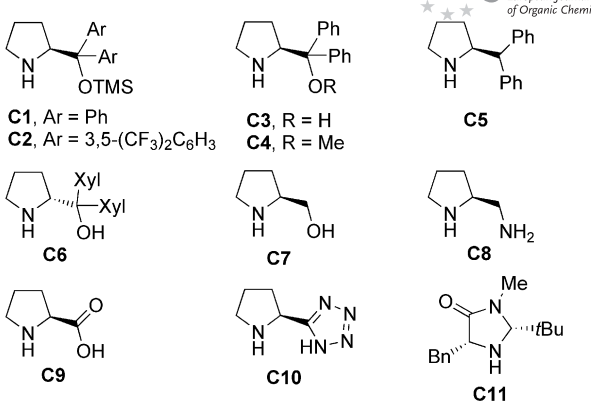


Figure 1. Structures of organocatalysts used in the screening reaction.

Table 1. Catalyst screening in the addition of benzyloxyacetaldehyde (**2**) to β-nitrostyrene (**1**).

Catalyst	Yield [%]	*syn*/*anti*[b]	*ee* (*syn*/*anti*)[c]
C1	86	54:46	95:93
C2	0	–	–
C3	24	56:44	95:84
C4	67	50:50	91:90
C5	69	50:50	74:40
C6	25	57:43	60:–
C7	36	52:48	95:57
C8	50	52:48	51:41
C9	≥10	50:50	–
C9[a]	44	83:17	61:–
C10	0	–	–
C11	0	–	–

[a] DMF was used as the solvent. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by HPLC on a Chiralpak AD-H column (**3** reduced to corresponding alcohol with $NaBH_4$).

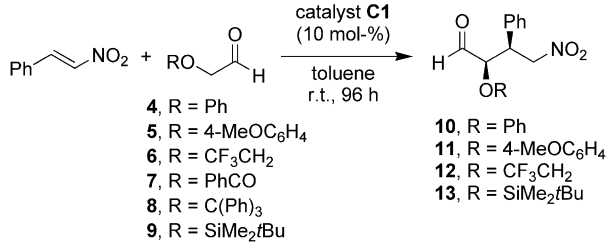
Having determined the most active catalyst, we continued in our investigation with organocatalyst **C1**. During optimization of the reaction conditions, we found that the solvent has a profound effect on the reaction. In solvents other than toluene, some or all reaction parameters were inferior. In more polar solvents, such as *i*PrOH, DMF, or CH_3CN, the *syn*/*anti* ratio improved; however, the yield and enantioselectivity decreased. The results of solvent screening are collected in Table 2.

Table 2. Addition of **2** to β-nitrostyrene catalyzed by **C1** in various solvents.

Solvent	Yield [%]	*syn*/*anti*[a]	*ee* (*syn*/*anti*)[b]
Toluene	86	54:46	95:93
Hexane	56	50:50	92:91
CH_2Cl_2	78	50:50	89:87
*i*PrOH	65	71:29	90:70
CF_3CH_2OH	25	58:42	90:67
DMF	37	67:33	95:76
CH_3CN	55	62:38	95:83
*t*BuOMe	≥10	50:50	–

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC on a Chiralpak AD-H column (**3** reduced to corresponding alcohol with $NaBH_4$).

The reaction is not restricted to benzyloxyacetaldehyde (**2**). Oxyacetaldehydes with various *O*-protecting groups were investigated. Aryl- and alkyl-substituted aldehydes **4**–**6** and silyl ether **9** were successfully added to **1** (Scheme 2). Resulting addition products **10**–**13** were isolated in medium to good yields. Aldehyde **7** with a benzoyl group and compound **8** with a sterically hindered trityl group did not afford the expected addition products. Additions of substituted oxyacetaldehydes to β-nitrostyrene are summarized in Table 3.



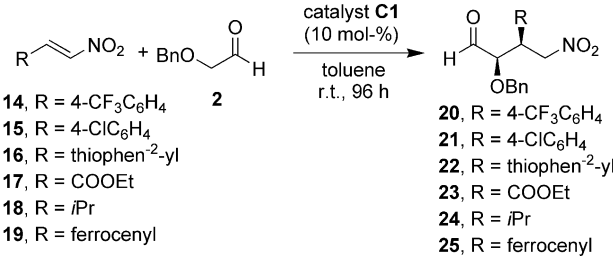
Scheme 2.

Table 3. Addition of substituted oxyacetaldehydes to β-nitrostyrene catalyzed by **C1**.

R	Yield [%]	*syn*/*anti*[a]	*ee* (*syn*/*anti*)[b]
Ph	58	61:39	96:96
4-$MeOC_6H_4$	73	54:46	94:94
CF_3CH_2	55	56:44	94:94
PhCO	0	–	–
Ph_3C	0	–	–
$SiMe_2tBu$	43	59:41	84:84

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC on a Chiralpak AD-H or OD-H column as the corresponding α,β-unsaturated ethyl ester after derivatization with ethyl(triphenylphosphoranylidene)acetate.

Benzyloxyaldehyde (**2**) also added well to other aromatic and heteroaromatic nitroalkenes **14**–**16** (Scheme 3). Ethyl 3-nitroacrylate (**17**) afforded product **23** in good yield (88%) and with high enantioselectivity (*syn* 95%*ee*, *anti* 93%*ee*; Scheme 3). In the same reaction under Hayashi's conditions,[20] the product was isolated in 85% yield with 92%*ee* (both diastereomers). The addition proceeded also with aliphatic nitroalkene **18** and ferrocenyl derivative **19**, but in these cases, products **24** and **25** were isolated only in low yields. Table 4 summarizes the screening of nitroolefins.



Scheme 3.

We also studied the reaction of β-nitrostyrene (**1**) with benzyloxyacetaldehyde (**2**) in the presence of catalyst **C1** by mass spectrometry. Aliquot samples were taken and analyzed by LC–HRMS. Iminium cation Int-**1** (*m*/*z* = 458.252) and the adduct of enamine to β-nitrostyrene (Int-**2**, *m*/*z* = 607.302) were observed. Figure 2 shows the mass spectrum and structures of the observed intermediates; the peak at *m*/*z* = 326.195 is catalyst **C1** and the peak at *m*/*z* = 236.144 is from the cation formed from catalyst **C1** after cleavage of the silyloxy group.

Table 4. Nitroalkenes **14**–**19** in the reaction with aldehyde **2**.

Nitroalkene	R	Yield [%]	*syn*/*anti*[a]	*ee* (*syn*/*anti*)[b]
14	4-$CF_3C_6H_4$	51	63:37	96:93
15	4-ClC_6H_4	95	54:46	96:95
16	thiophen-2-yl	88	60:40	93:91
17	COOEt	88	71:29	95:93
18	*i*Pr	30	79:21	82:93[c]
19	ferrocenyl	14	56:44	–

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by HPLC on a Chiralpak AD-H or OD-H column as the corresponding α,β-unsaturated ethyl ester after derivatization with ethyl(triphenylphosphoranylidene)acetate. [c] Determined by HPLC on a Chiralpak IC column as the corresponding alcohol.

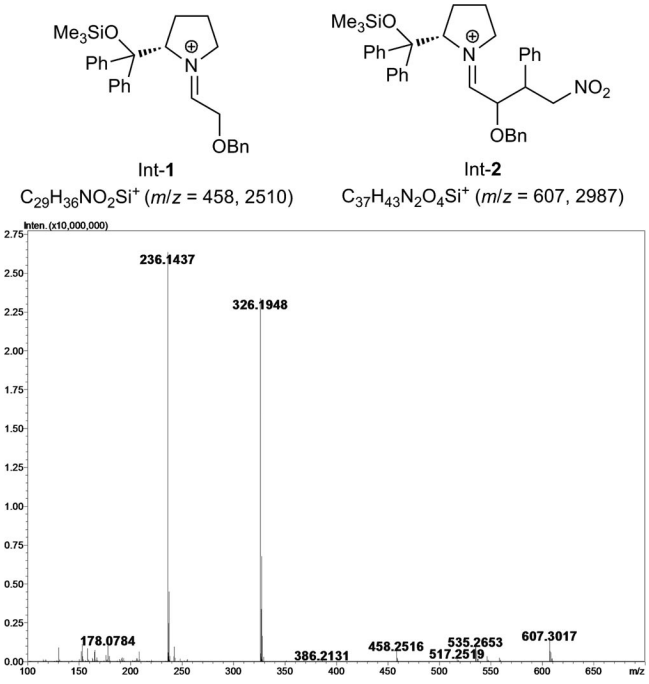


Figure 2. High-resolution mass spectrum of the reaction of β-nitrostyrene with aldehyde **2** and catalyst **4** after 4 h.

The low diastereoselectivity for the addition of aldehyde **2** to β-nitrostyrene can be explained by formation of both (*E*)- and (*Z*)-enamine from the aldehyde and the catalyst. DFT calculations support this notion, as there is only a small energy difference (2.9 kJ/mol) between these enamines. All calculations were performed in the Spartan 08 program.[23] A conformational search was performed by molecular mechanics; three lowest-energy conformers were further refined by the semiempirical AM1 method and finally geometrical optimization was performed by DFT by using the B3LYP functional and the 6-31G* basis set.[24]

Single-point energy calculation on the lowest-energy conformer was then performed by using the 6-311+G** basis set. Figure 3 shows the DFT-optimized structures of the (*E*) and (*Z*)-enamine intermediates formed from catalyst **C1** and aldehyde **2**.

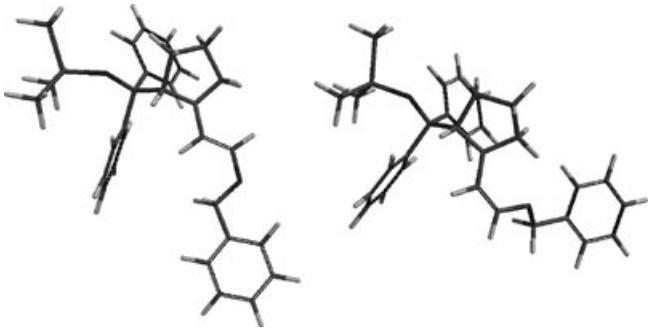


Figure 3. Optimized structures of the (*E*)- and (*Z*)-enamines from catalyst **C1** and aldehyde **2**.

Another at least partial reason for the deterioration of the diastereoselectivity is probably epimerization of the product by the catalyst. To verify this idea, compound **3** (*syn*/*anti*, 67:33) was stirred in toluene in the presence of catalyst **C1** (10 mol-%) for 72 h. Subsequent ^{1}H NMR spectroscopic analysis of diastereomers of **3** showed an *syn*/*anti* ratio of 53:47. We believe that both the small energy difference between the enamines and product epimerization contribute to the low diastereoselectivity of the reaction.

On the basis of Seebach's earlier work on the Michael addition of achiral enamines to nitroolefins,[25] we propose an open-transition-state model to explain the course of the reaction of benzyloxyacetaldehyde (**2**) with β-nitrostyrene (**1**, Figure 4). On the basis of our calculations we suppose that the enamine formed from aldehyde **2** and catalyst **C1** adopts a more favorable *anti* arrangement with respect to the large trimethylsilyloxy(diphenyl)methyl group. Seebach's recent X-ray studies on the reaction of phenylacetaldehyde enamine with **C1** also support this supposition.[26] Chiral catalyst (*S*)-**C1** shields the *Si* face of the corresponding enamine. The nitroolefin will then approach it from the *Re* face. The (*E*)- and (*Z*)-enamine will then give rise to (*R*,*S*)- and (*S*,*S*)-**3**.

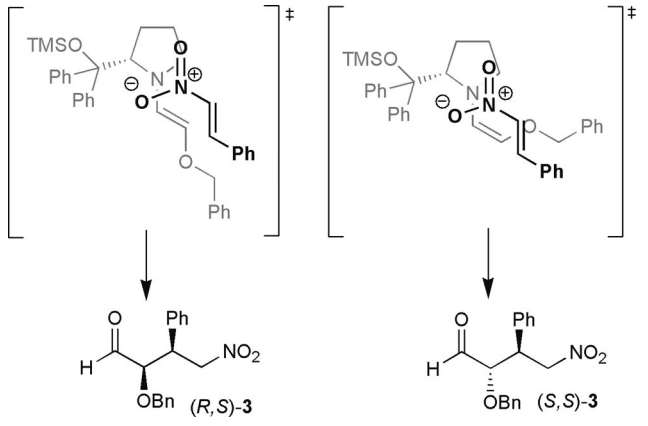


Figure 4. Proposed transition-state model.

Conclusions

We have developed methodology for the enantioselective addition of oxyacetaldehydes to nitroalkenes. Although the resulting products were isolated as diastereomeric mixtures, chemical yields were good as were the enantioselectivities (up 96%*ee*).

Experimental Section

General: Solvents were dried and purified by standard methods before use. NMR spectra were recorded with a Varian NMR System 300 instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C). Chemical shifts (δ) are given in ppm relative to tetramethylsilane. Flash chromatography was performed on Merck silica gel 60. Thin-layer chromatography was performed on Merck TLC-plates silica gel 60, F-254. Enantiomeric excesses were determined by HPLC on a Chiralpak AD-H, AS-H, or IC column or on a Chiralcel OD-H (Daicel Chemical Industries) column by using hexane/*i*PrOH as the mobile phase and UV detection. HRMS analyses were performed with a LC-IT-TOF MS (Shimadzu, Kyoto, Japan) by using an Ascentis C18 column with gradient H_2O/acetonitrile elution over 33 min. Racemic mixtures of all the products were prepared according to the general procedure by using morpholine as the catalyst.

Typical Procedure: Benzyloxyacetaldehyde (**2**; 100 mg, 0.666 mmol) was added to a solution of β-nitrostyrene (**1**; 496 mg, 3.32 mmol) and (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (**C1**; 21.5 mg, 0.066 mmol) in toluene (1 mL) at room temperature. The reaction mixture was stirred for 96 h at room temperature. The solution was diluted with CH_2Cl_2 (10 mL) and washed with water. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (SiO_2, EtOAc/hexane, 1:7 to 1:5) provided Michael adduct **3** as a pale-orange oil.

HPLC Analyses: Enantiomeric purities of the products of the Michael addition of oxyacetaldehydes to nitroolefins are difficult to analyze by HPLC. Therefore, these compounds were derivatized before analysis. Products **3**, **10**, and **24** were reduced to the corresponding alcohol with $NaBH_4$ (4 equiv.) in MeOH (8 mL) at 0 °C for 1.5 h. The reaction was quenched with 5% HCl. The aqueous layer was extracted with Et_2O (3 × 8 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Flash chromatography (SiO_2, EtOAc/*n*-hexane, 1:5 to 1:3) afforded the product as a pale-orange–yellow oil. Products **11**–**13** and **20**–**23** were derivatized with ethyl(triphenylphosphoranylidene)acetate (1.5 equiv.) to the corresponding α,β-unsaturated ethyl esters at room temperature in benzene (2 mL) for 4 h. The crude reaction mixture was concentrated under reduced pressure. Flash chromatography (SiO_2, EtOAc/*n*-hexane, 1:5) afforded the product as a colorless oil.

2-(Benzyloxy)-4-nitro-3-phenylbutanal (3): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.51, 9.41 (d, J = 1.5 Hz, 1 H, CHO), 7.21–7.39 (m, 10 H, 2 Ph), 4.85 (m, 1 H, CH_2NO_2), 4.77 (dd, J = 7.0, 18.7 Hz, 1 H, PhCH_2O), 4.65 (dd, J = 12.0, 17.3 Hz, 1 H, PhCH_2O), 4.52 (dd, J = 11.5, 14.0 Hz, 1 H, CH_2NO_2), 4.09 (dd, J = 1.6, 4.3 Hz, 1 H,

OC*H*CHO), 3.99 (m, 1 H, PhCH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.7 (CHO), 200.3 (CHO), 136.6 (C_{Ar}), 136.4 (C_{Ar}), 135.3 (C_{Ar}), 134.2 (C_{Ar}), 128.5 (C_{Ar}), 84.1, 82.6 (*C*HCHO), 76.3, 76.2 (CH_2NO_2), 74.0, 73.5 ($PhCH_2O$), 45.3, 44.8 (Ph*C*H) ppm. HRMS: calcd. for $C_{17}H_{16}NO_4$ [M – H]$^-$ 298.108; found 298.079. HPLC (AD-H, *i*PrOH/*n*-hexane = 5:95, 1 mL/min, λ = 217 nm): t_R = 71.2 (*syn*-minor), 60.8 (*syn*-major), 46.7 (*anti*-major), 43.6 (*anti*-minor) min.

4-Nitro-3-phenyl-2-(phenyloxy)butanal (10): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.61, 9.40 (d, *J* = 1.8 Hz, 1 H, CHO), 7.34 (m, 8 H, Ph), 6.88 (m, 2 H, Ph), 5.00, 4.98 (dd, *J* = 8.1, 13.5 Hz, 1 H, CH_2NO_2), 4.83–4.87 (m, 1 H, C*H*CHO), 4.79 (dd, *J* = 7.1, 13.4 Hz, 1 H, CH_2NO_2), 4.15–4.20 (m, 1 H, PhCH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.8, 199.7 (CHO), 129.4 (C_{Ar}), 122.8 (C_{Ar}), 115.4 (C_{Ar}), 82.5, 81.0 (*C*HCHO), 75.8 (CH_2NO_2), 45.2, 44.8 (Ph*C*H) ppm. HRMS: calcd. for $C_{16}H_{14}NO_4$ [M – H]$^-$ 284.092; found 284.065. HPLC (Chiralpak AD-H, *i*PrOH/*n*-hexane = 5:95, 1 mL/min, λ = 217 nm): t_R = 41.9 (*syn*-minor), 39.0 (*anti*-minor), 36.1 (*syn*-major), 33.6 (*anti*-major) min.

2-(4-Methoxybenzyloxy)-4-nitro-3-phenylbutanal (11): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.48, 9.37 (d, *J* = 1.6 Hz, 1 H, CHO), 7.28 (m, 5 H, Ph), 6.89 (m, 4 H, MeO*Ph*), 4.82 (dd, *J* = 8.4, 13.1 Hz, 1 H, CH_2NO_2), 4.68 (dd, *J* = 5.2, 12.7 Hz, 1 H, PhC*H*$_2$O), 4.61 (dd, *J* = 4.0, 9.0 Hz, 1 H, PhC*H*$_2$O), 4.46 (dd, *J* = 11.3, 17.0 Hz, 1 H, CH_2NO_2), 4.06 (dd, *J* = 1.5, 4.3 Hz, 1 H, C*H*CHO), 3.96 (m, 1 H, PhC*H*), 3.81 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.7, 200.2 (CHO), 159.8 (CH_3OC_{Ar}), 135.2 (C_{Ar}), 134.0 (C_{Ar}), 129.2 (C_{Ar}), 114.1 (C_{Ar}), 83.5, 82.1 (*C*HCHO), 76.3, 76.2 (CH_2NO_2), 73.5, 73.0 (CH_2O), 55.3 (OCH_3), 45.1, 44.7 (Ph*C*H) ppm. HRMS: calcd. for $C_{18}H_{18}NO_5$ [M – H]$^-$ 328.119; found 328.086. HPLC (Chiralpak AD-H, *i*PrOH/*n*-hexane = 5:95, 0.75 mL/min, λ = 217 nm): t_R = 32.6 (*anti*-minor), 28.5 (*syn*-minor), 21.8 (*anti*-major), 20.2 (*syn*-major) min.

4-Nitro-3-phenyl-2-(2,2,2-trifluoroethoxy)butanal (12): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.51 (d, *J* = 1.2 Hz, 1 H, CHO), 9.46 (s, 1 H, CHO), 7.21–7.38 (m, 5 H, Ph), 4.96 (dd, *J* = 8.8, 13.4 Hz, 1 H, CH_2NO_2), 4.85 (dd, *J* = 6.0, 13.5 Hz, 1 H, CF_3CH_2O), 4.77 (dd, *J* = 8.4, 13.5 Hz, 1 H, CF_3CH_2O), 4.68 (dd, *J* = 6.5, 13.4 Hz, 1 H, CH_2NO_2), 4.05–4.12 (m, 1 H, C*H*CHO), 3.82–3.88 (m, 1 H, PhC*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.3 (CHO), 198.1 (CHO), 134.5 (C_{Ar}), 133.2 (C_{Ar}), 128.9 (C_{Ar}), 128.0 (CF_3), 86.1, 84.8 (*C*HCHO), 75.7, 75.5 (CH_2NO_2), 68.6 (CF_3*C*H$_2$), 44.6, 44.5 (Ph*C*H) ppm. HRMS: calcd. for $C_{12}H_{11}F_3NO_4$ [M – H]$^-$ 290.064; found 290.036. HPLC (Chiralpak AD-H, *i*PrOH/*n*-hexane = 4:96, 0.45 mL/min, λ = 217 nm): t_R = 95.6 (*syn*-minor), 87.3 (*anti*-minor), 70.9 (*syn*-major), 66.3 (*anti*-major) min.

2-(*tert*-Butyldimethylsilyloxy)-4-nitro-3-phenylbutanal (13): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.56, 9.35 (d, *J* = 1.44 Hz, 1 H, CHO), 7.29 (m, 5 H, Ph), 4.87 (dd, *J* = 8.3, 13.4 Hz, 1 H, CH_2NO_2), 4.78 (m, 2 H, C*H*CHO), 4.68 (dd, *J* = 6.9, 13.4 Hz, 1 H, CH_2NO_2), 3.97 (m, 1 H, PhCH), 0.95, 0.92 [s, 9 H, C(CH_3)$_3$], 0.064, 0.057 (s, 3 H, 2 CH_3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 23 °C): δ = 202.5, 201.2 (CHO), 135.8, 134.2 (C_{Ar}), 129.0 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 79.5, 77.3 (*C*HCHO), 75.9, 75.0 (CH_2NO_2), 46.0 (Ph*C*H), 25.7 [(*C*H$_3$)$_3$C], 25.6 [(CH$_3$)$_3$*C*], 18.1 (CH_3) ppm. HRMS: calcd. for $C_{16}H_{24}NO_4Si$ [M – H]$^-$ 322.148; found 322.148. HPLC (Chiralpak IC, *i*PrOH/*n*-hexane = 5:95, 0.5 mL/min, λ = 217 nm): t_R = 44.8 (*anti*-minor), 22.9 (*syn*-major), 20.4 (*anti*-major), 16.9 (*syn*-minor) min.

2-(Benzyloxy)-4-nitro-3-(4-trifluoromethylphenyl)butanal (20): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.59, 9.43 (d, *J* = 1.8 Hz, 1 H, CHO), 7.58 (m, 2 H, H_{Ar}), 7.38 (m, 7 H, H_{Ar}), 4.83 (m, 1 H, CH_2NO_2), 4.78 (m, 1 H, $PhCH_2$), 4.66 (m, 1 H, $PhCH_2$), 4.58 (m, 1 H, CH_2NO_2), 4.53 (m, 1 H, C*H*CHO), 4.06 (m, 1 H, ArCH) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 202.0, 200.2 (CHO), 138.2 (C_{Ar}), 136.0 (C_{Ar}), 129.6 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 125.9 (CF_3), 83.7, 82.2 (*C*HCHO), 76.0, 75.2 (CH_2NO_2), 74.0, 73.7 (CH_2O), 44.8, 44.3 (ArCH) ppm. HRMS: calcd. for $C_{18}H_{15}F_3NO_4$ [M – H]$^-$ 366.095; found 366.095. HPLC (Chiralpak AD-H, *i*PrOH/*n*-hexane = 5:95, 0.8 mL/min, λ = 217 nm): t_R = 64.8 (*syn*-minor), 51.8 (*anti*-minor), 33.2 (*anti*-major), 24.5 (*syn*-major) min.

2-(Benzyloxy)-3-(4-chlorophenyl)-4-nitrobutanal (21): ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 9.55, 9.44 (d, *J* = 1.9 Hz, 1 H, CHO), 7.25 (m, 9 H, H_{Ar}), 4.88 (dd, *J* = 4.7, 8.5 Hz, 1 H, CH_2NO_2), 4.76 (dd, *J* = 1.5, 3.9 Hz, 1 H, $PhCH_2O$), 4.69 (m, 1 H, $PhCH_2$), 4.52 (dd, *J* = 11.5, 15.8 Hz, 1 H, CH_2NO_2), 4.07 (dd, *J* = 1.4, 4.15 Hz, 1 H, C*H*CHO), 3.99 (m, 1 H, PhCH) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 202.2, 200.2 (CHO), 132.5 (ClC_{Ar}), 128.4–129.5 (C_{Ar}), 83.8, 82.2 (*C*HCHO), 76.1, 75.6 (CH_2NO_2), 73.9, 73.6 (CH_2O), 44.5, 43.9 (Ph*C*H) ppm. HRMS: calcd. for $C_{17}H_{15}ClNO_4$ [M – H]$^-$ 332.069; found 332.069. HPLC (Chiralpak AD-H, *i*PrOH/*n*-hexane = 5:95, 0.8 mL/min, λ = 217 nm): t_R = 71.5 (*syn*-minor), 54.4 (*anti*-minor), 36.6 (*anti*-major), 32.9 (*syn*-major) min.

2-(Benzyloxy)-4-nitro-3-(thiophen-2-yl)butanal (22): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.57, 9.48 (d, *J* = 1.9 Hz, 1 H, CHO), 7.37 (m, 5 H, Ph), 7.25 (m, 1 H, H_{thio}), 6.97 (m, 1 H, H_{thio}), 6.93 (m, 1 H, H_{thio}), 4.56–4.86 (m, 4 H, CH_2NO_2, $PhCH_2$), 4.35 (m, 1 H, C*H*CHO), 4.05 (m, 1 H, CH) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 23 °C): δ = 202.7, 199.8 (CHO), 137.2, 136.3 (C_{thio}), 134.9 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 127.14 (C_{thio}), 126.8 (C_{thio}), 126.6 (C_{thio}), 83.9, 81.7 (*C*HCHO), 76.8, 76.7 (CH_2NO_2), 73.9, 73.7 (CH_2O), 40.9, 40.2 (CH_{thio}) ppm. HRMS: calcd. for $C_{15}H_{14}NO_4S$ [M – H]$^-$ 304.064; found 304.064. HPLC (Chiralpak AS-H, *i*PrOH/*n*-hexane = 3:97, 0.8 mL/min, λ = 217 nm): t_R = 72.2 (*anti*-minor), 65.8 (*anti*-major), 58.5 (*syn*-major), 50.9 (*syn*-minor) min.

Ethyl 3-(Benzyloxy)-2-(nitromethyl)-4-oxobutanoate (23): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.70 (s, 1 H, CHO), 9.66 (d, *J* = 0.8 Hz, 1 H, CHO), 7.30–7.42 (m, 5 H, Ph), 4.86 (dd, *J* = 7.4, 14.6 Hz, 1 H, CH_2NO_2), 4.79 (d, *J* = 11.8 Hz, 1 H, PhC*H*$_2$O), 4.63 (d, *J* = 11.8 Hz, 1 H, PhC*H*$_2$O), 4.40 (dd, *J* = 6.0, 14.6 Hz, 1 H, CH_2NO_2), 4.20 (m, 2 H, C*H*$_2$CH$_3$), 4.06 (d, *J* = 3.5 Hz, 1 H, C*H*CHO), 3.85, 3.71 (ddd, *J* = 3.5, 6.0, 7.5 Hz, 1 H, EtO_2CCH), 1.25, 1.23 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.3 (CHO), 199.2 (CHO), 169.1 (*C*OOEt), 167.9 (*C*OOEt), 135.0 (C_{Ar}), 135.9 (C_{Ar}), 128.8 (C_{Ar}), 80.1, 80.2 (*C*HCHO), 73.7 (Ph*C*H$_2$), 71.8, 70.9 (CH_2NO_2), 62.3 (O*C*H$_2$CH$_3$), 44.8, 43.7 (EtOOC*C*H), 13.9 (CH$_2$*C*H$_3$) ppm. HRMS: [M]$^+$ calcd. for $C_{17}H_{17}NO_4$ not visible. HRMS: calcd. for $C_{16}H_{16}NO_3$ [M – CO]$^-$ 299.113; found 299.993. HPLC (Chiralcel OD-H, *i*PrOH/*n*-hexane = 10:90, 0.9 mL/min, λ = 217 nm): t_R = 43.2 (*syn*-minor), 29.2 (*anti*-minor), 24.7 (*syn*-major), 19.8 (*anti*-major) min.

2-(Benzyloxy)-3-ethyl-4-methylpentanal (24): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.55, 9.44 (d, *J* = 1.2 Hz, 1 H, CHO), 7.35 (m, 9 H, H_{Ar}), 4.74 (d, *J* = 11.6 Hz, 1 H, CH_2NO_2), 4.54 (d, *J* = 11.5 Hz, 1 H, CH_2NO_2), 4.48 (m, 2 H, $PhCH_2$), 3.90, 3.87 (dd, *J* = 1.2, 4.2 Hz, 1 H,C*H*CHO), 2.69 (m, 1 H, *i*PrCH), 1.92 (m, 1 H, Me_2CH), 0.97, 0.93 (d, *J* = 6.8 Hz, 2 CH_3) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 202.8, 202.0 (CHO), 136.7 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 83.0, 82.2 (*C*HCHO), 73.8, 73.7 (CH_2NO_2), 73.3, 72.9 (CH_2O), 45.2, 43.8 (*i*PrCH), 28.3, 27.1 (Me_2CH), 19.9, 19.4 (2 CH_3) ppm. HRMS: calcd. for $C_{14}H_{18}NO_4$ [M – H]$^-$ 264.124; found 264.124. HPLC (Chiralpak IC, *i*PrOH/*n*-hexane = 8:92, 0.5 mL/

min, λ = 217 nm): t_R = 79.3 (*syn*-minor), 70.2 (*anti*-minor), 60.6 (*syn*-major), 56.5 (*anti*-major) min.

2-(Benzyloxy)-3-(ferrocenyl)-4-nitrobutanal (25): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.47, 9.58 (d, J = 1.8 Hz, 1 H, CHO), 7.27–7.39 (m, 5 H), 4.97–4.75 (m, 2 H, $PhCH_2O$), 4.67 (dd, J = 8.1, 12.0 Hz, 1 H, CH_2NO_2), 4.53 (dd, J = 6.3, 12.0 Hz, 1 H, CH_2NO_2), 4.19–4.13 (m, 7 H, Fc), 4.05–3.92 (m, 3 H), 3.81 (m, 1 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 203.14 (CHO), 201.68 (CHO), 136.5 (C_{Ar}), 136.4 (C_{Ar}), 128.64 (2 CH_{Ar}) 128.62 (2 CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (2 CH_{Ar}), 85.3 (CH), 84.8 (CH), 82.8 (CH), 82.3 (CH), 77.3 (C), 76.2 (CH_2), 75.9 (CH_2), 73.5 (CH_2), 73.1 (CH_2), 68.98 (CH), 68.92 (5 CH), 68.90 (5 CH), 68.5 (CH), 68.33 (CH), 68.30 (CH), 68.0 (CH), 67.9 (CH), 66.9 (CH), 66.8 (CH) ppm. HRMS: calcd. for $C_{21}H_{21}FeNO_4$ $[M - H]^-$ 406.075; found 406.077.

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