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# Catalytic asymmetric Henry reactions of silyl nitronates with aldehydes

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A catalytic enantioselective Henry reaction of silyl nitronates with aldehydes has been developed. Different chiral Lewis acids have been tested for the reaction and it has been found that a variety of chiral copper–ligand complexes can catalyze the Henry reaction. The best yield, diastereo- and enantioselectivity of the nitroalcohols formed are obtained by the application of a copper(II)–diphenyl–bisoxazoline complex as the catalyst in the presence of tetrabutylammonium triphenylsilyldifluorosilicate (TBAT). In order to minimize the epimerization of the nitroaldol products they were converted into the corresponding Mosher esters. The reaction proceeds well for different aromatic aldehydes reacting with alkyl nitronates.

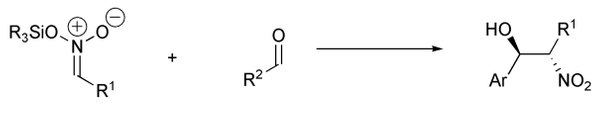
## Introduction

β-Hydroxynitroalkanes, prepared by the Henry (nitroaldol) reaction, are valuable synthetic intermediates in organic synthesis.[1]

The development of catalytic enantioselective versions of the nitroaldol reaction has recently been in focus. Sibasaki *et al.* have shown that the use of heterobimetallic complexes with lanthanide BINOL systems provide an efficient catalyst for the Henry reaction of nitromethane with different types of aldehydes.[2] Catalytic enantioselective nitroaldol reactions of nitromethane with aldehydes have also been developed by Trost *et al.* by the use of a chiral dinuclear catalyst to obtain impressive enantioselectivities.[3] Our approach to catalytic enantioselective nitroaldol reactions has been the development of the highly enantioselective addition of nitromethane to α-ketoesters catalyzed by a chiral *tert*-butyl bisoxazoline copper(II) complex.[4] This turned out to be a quite general reaction for many different α-ketoesters and provided an easy entry to optically active β-nitro-α-hydroxy esters and β-amino-α-hydroxy esters.

One of the drawbacks for the catalytic enantioselective nitroaldol reaction developed is that it is mainly restricted to nitromethane acting as the nucleophile, with the exception of the lanthanide–lithium–BINOL complex which can also catalyse the reaction of alkyl aldehydes with other nitroalkanes.[2e]

An alternative approach to the Henry reaction is the application of silyl nitronates **1** instead of nitro compounds for the addition to aldehydes **2** (Scheme 1). Seebach *et al.*




**1** **2** **3**

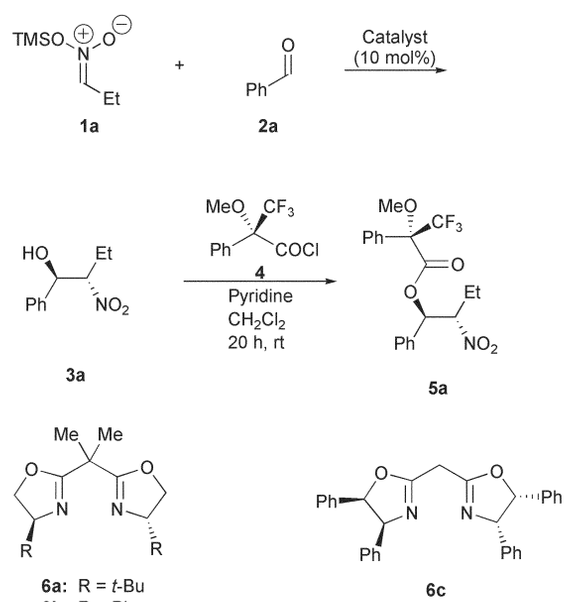
**Scheme 1** The silyl nitronate Henry reaction.

have described the diastereoselective fluoride catalyzed addition of silyl nitronates to aldehydes.[5] Recently, we described the asymmetric addition of silyl nitronates to imines in the presence of catalytic amounts of chiral Lewis acids.[6]

In this paper we present the development of a catalytic diastereo- and enantioselective nitroaldol reaction of nitronates **1** with aldehydes **2** in the presence of chiral Lewis complexes.

## Results and discussion

The nitroaldol reaction of the nitronate **1a** with benzaldehyde **2a** proceeds well in the presence of different chiral Lewis acid complexes as the catalyst and the nitroalcohol **3a** can be obtained (Scheme 2). However, the isolation and characterization of the nitroalcohol **3a** obtained in the present type of reaction turned out to be tedious, since this compound is unstable and tends to epimerize and undergo a retro-Henry reaction.[7] Thus compound **3a** was subsequently converted into the Mosher ester **5a** by reaction with (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride ((*S*)-MTPA-Cl), **4**. The Mosher esters **5** are stable compounds and were isolated. The enantiomeric excess[7] of the nitroaldol reaction was determined from the diastereomeric excess of the Mosher esters.




**Scheme 2** Catalytic diastereo- and enantioselective nitroaldol reaction of nitronates **1a** with aldehydes **2a**, and subsequent conversion into the Mosher ester **5a**.

Among a series of different chiral ligands BINAP and 1,2-bis((2*S*,5*S*)-2,5-dimethylphospholano)benzene (DUPHOS) (*P*,*P*-chelating), bisoxazolines (BOX) and Py–BOX (*N*,*N*-chelating), and phosphinoxazoline (*N*,*P*-chelating) and dibenzofuradiylphenyloxazoline (DBFOX) the BOX ligands **6a**–**c** gave the most promising results.

In Table 1 is presented some of the screening results for the nitroaldol reaction of nitronate **1a** with benzaldehyde **2a**

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**Table 1** Nitroaldol reaction of nitronate **1a** with benzaldehyde **2a** in the presence of different copper salts and the BOX ligands **6a**–**c** (10 mol%) under various reaction conditions at −78 °C and the subsequent conversion of the nitroaldol to the Mosher ester **5a**

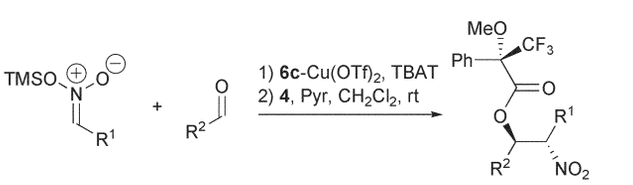
| Entry | Catalyst | Solvent | Conv. (%) | Dr *threo* : *erythro* | Ee[a] *threo*(%) |
|---|---|---|---|---|---|
| 1 | **6a**-$Cu(OTf)_2$ | THF | 51 | 3 : 1 | 19 |
| 2 | **6b**-$Cu(OTf)_2$ | THF | 66 | 3.5 : 1 | 0 |
| 3 | **6c**-$Cu(OTf)_2$ | THF | 70 | 1.2 : 1 | 66 |
| 4 | **6c**-$Cu(OTf)_2$ | $CH_2Cl_2$ | 73 | 1.1 : 1 | 35 |
| 5 | **6c**-$Cu(OTf)_2$ | $Et_2O$ | 68 | 1.2 : 1 | 56 |
| 6 | **6c**-$Cu(SbF_6)_2$ | $CH_2Cl_2$ | 73 | 1.1 : 1 | 35 |
| 7 | **6c**-$CuPF_6$ | THF | 70 | 1.5 : 1 | 20 |
| 8 | **6c**-$CuClO_4$ | THF | 69 | 1 : 1 | 30 |
| 9 | **6c**-$Cu(OTf)_2$[b] | THF | 94 | 5 : 1 | 65 |

[a] The ee of the nitroaldol reaction is derived from the de of the Mosher ester. [b] 20 mol% of the catalyst was applied in the presence of 20 mol% tetrabutylammonium triphenylsilyldifluorosilicate (TBAT) and the reaction was performed at room temperature.

catalyzed by different copper salts and applying the BOX ligands **6a**–**c** under various reaction conditions.

Among the Lewis acids tested for the reaction both copper(I) and copper(II) salts showed the most promising properties, as a good conversion was found with these salts. The results in Table 1 for the reaction in the presence of the chiral BOX ligands **6a**–**c** show that the corresponding Mosher ester is obtained with a low *threo : erythro* ratio, but as it appears from the results this selectivity is very dependent of both the ligand and the solvent. The highest enantiomeric excess is obtained when applying the bis[(4*R*,5*S*)-diphenyloxazoline] ligand **6c** in combination with Cu(II) salts where up to 66% ee is found (entry 3). The reaction presented in entry 3, Table 1 has also been performed at 0 °C and room temperature, and under these conditions the conversion was 85% and 94%, the diastereomeric ratio 2 : 1 and 5 : 1, respectively, and the enantioselectivity was in both cases 65% ee of *threo*-**5a**. The results obtained for the reaction in the presence of **6c**–$CuClO_4$ were not promising (entry 8). When the reaction was performed in the presence of 20 mol% of **6c**–$Cu(TfO)_2$ and the fluoride donor tetrabutylammonium triphenylsilyldifluorosilicate (TBAT),[8] the reaction proceeded at room temperature and the results were improved with respect to both conversion, *threo*-selectivity and enantioselectivity (entry 9). The enantiomeric excess of the *erythro*-isomer was in all cases lower than that of the obtained *threo*-isomer.

To develop this reaction for other silyl nitronates and aldehydes the nitroaldol reaction was performed using nitronates **1a**,**b** and aldehydes **2a**–**g** in the presence of **6c**–$Cu(TfO)_2$ as the catalyst and TBAT in THF (Scheme 3,




**1a:** $R^1$ = Et
**1b:** $R^1$ = Pentyl

**2a:** $R^2$ = Ph
**2b:** $R^2$ = *p*-$MeOC_6H_4$
**2c:** $R^2$ = *p*-$NCC_6H_4$
**2d:** $R^2$ = *p*-$O_2NC_6H_4$
**2e:** $R^2$ = *m*-$O_2NC_6H_4$
**2f:** $R^2$ = 2-Np
**2g:** $R^2$ = (*E*)-Ph-CH=CH

**5a:** $R^1$ = Et, $R^2$ = Ph
**5b:** $R^1$ = Et, $R^2$ = *p*-$MeOC_6H_4$
**5c:** $R^1$ = Et, $R^2$ = *p*-$NCC_6H_4$
**5d:** $R^1$ = Et, $R^2$ = *p*-$O_2NC_6H_4$
**5e:** $R^1$ = Et, $R^2$ = *m*-$O_2NC_6H_4$
**5f:** $R^1$ = Et, $R^2$ = 2-Np
**5g:** $R^1$ = Pentyl, $R^2$ = Ph
**5h:** $R^1$ = Et, $R^2$ = (*E*)-Ph-CH=CH

**Scheme 3** Catalytic diastereo- and enantioselective nitroaldol reaction of nitronates **1** with aldehydes **2**.

Table 2). The crude nitroaldol compounds obtained from the first step of the reaction were subsequently converted to the Mosher esters after filtration and evaporation of the solvent.

The nitronate **1a**, derived from nitropropane, reacts well with the different aldehydes and the nitroalcohols are obtained with moderate to very high diastereoselectivity. For the aromatic aldehydes, substituted with electron-withdrawing substituents (**2c**–**e**) only the *threo*-isomer could be detected (Table 2, entries 3-6). However, for these substrates the enantioselectivity of the reactions is moderate. The reaction of the nitronates **1a**,**b** with benzaldehyde **2a** and *p*-methoxybenzaldehyde **2b** proceeds with lower diastereoselectivity, however, the enantioselectivity of the nitroalcohols **3a**,**b**,**g** are improved (entries 1,2,7) compared to those substituted with electron-withdrawing substituents.

The enantiomeric excess of the nitroaldol reactions listed in Table 2 are derived from the de of the obtained Mosher ester and the highest ee obtained so far is 65%. In all of the entries where the *erythro*-isomers were detected the ee's of the *erythro*-isomers were lower than those obtained for the corresponding *threo*-isomer. $^1$H NMR analysis of the crude nitroaldols obtained in the reactions show higher ratios of the *erythro*-isomer than observed after conversion into the Mosher esters. This strongly indicates that the unstable nitroaldols undergo partial epimerization before being converted into the stable Mosher esters **5a**–**h**. We thus have reason to believe that the ee's of the Henry reaction, derived from the de's of the Mosher esters, represent the minimal ee's actually induced in the reaction.

In summary we have developed the first catalytic asymmetric Henry reaction of silyl nitronates with aldehydes. This is made possible by trapping the unstable nitroaldols using (*S*)-MTPA-Cl to form the corresponding Mosher esters **5a**–**h**. For several of the entries good yields, high *threo*-selectivities and moderate enantioselectivities were obtained. In future work we will try to completely avoid epimerization of the crude nitroaldols, which will reveal if higher enantioselectivities can be obtained by this approach.

## Experimental

### General methods

Commercially available starting materials were used without further purification. Solvents were dried according to standard procedures. Purification of the products was carried out by flash chromatography (FC) using Merck silica gel 60 (230–400 mesh). $^1$H and $^{13}$C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as the solvent and were reported in ppm downfield from TMS ($\delta = 0$) for $^1$H NMR and relative to the central $CDCl_3$ resonance ($\delta$ = 77.00) for $^{13}$C NMR. Mass spectra and high resolution mass spectra were obtained on an LC-TOF spectrometer (Micromass). All glassware was dried at 120 °C for 24 h and flame dried before use. $Cu(SbF_6)_2$ was made by mixing $CuBr_2$ with $AgSbF_6$ in $CH_2Cl_2$. The solution was filtered through Celite before use. The silyl nitronates **1a** and **1b** were synthesized from the corresponding nitro compounds and trimethylsilyl chloride according to literature procedures.[9] All other reagents and materials were purchased from Aldrich or Lancaster.

### Preparation of catalyst 6c–Cu(OT f)$_2$

2,2′-Methylenebis[(4*R*,5*S*)-4,5-diphenyl-2-oxazoline] (20.18 mg, 0.044 mmol, 22 mol%) and $Cu(OTf)_2$ (14.4 mg, 0.04 mmol,

**Table 2** Nitroaldol reaction of nitronates **1a**,**b** with different aldehydes **2a**–**g** in the presence of **6c**–$Cu(OTf)_2$ (20 mol%) as the catalyst and tetrabutylammonium triphenylsilyldifluorosilicate (TBAT) (20 mol%) in THF as the solvent at room temperature

| Entry | Nitronate | Aldehyde | Yield (%) | Dr *threo* : *erythro* | Ee[a] *threo* (%) |
|---|---|---|---|---|---|
| 1 | **1a** | **2a** | **5a** – 76 | 5 : 1 | 65 |
| 2 | **1a** | **2b** | **5b** – 34 | 3 : 1 | 59 |
| 3 | **1a** | **2c** | **5c** – 47 | >10 : 1 | 40 |
| 4 | **1a** | **2d** | **5d** – 63 | >10 : 1 | 50 |
| 5 | **1a** | **2e** | **5e** – 67 | >10 : 1 | 45 |
| 6 | **1a** | **2f** | **5f** – 34 | 2.5 : 1 | 60 |
| 7 | **1b** | **2a** | **5g** – 81 | 3 : 1 | 43 |
| 8 | **1a** | **2g** | **5h** – 44 | >10 : 1 | 45 |

[a] The ee of the nitroaldol reaction is derived from the de of the Mosher ester.

20 mol%) were mixed and stirred under vacuum for 30 min. After adding THF (2 mL) and stirring for 10 min, TBAT (21.6 mg, 0.040 mmol, 20 mol%) in THF (0.5 mL) was added and stirring was continued for 10 min.

### General procedure for the asymmetric Henry reaction of nitronates 1a–b and aldehydes 2a–g to obtain the Mosher esters 5a–h

To catalyst **6c**–$Cu(OTf)_2$ prepared as described above was added the aldehyde (0.2 mmol) and after adjusting the reaction mixture to the appropriate temperature the TMS–nitronate (0.3 mmol) was added and the reaction was stirred at room temperature for 16 h. Then the solvent was removed by evaporation and to the residue was added $CH_2Cl_2$ (0.6 mL), pyridine (0.6 mL, 8 mmol) and (*S*)-MTPA-Cl (45 μL, 0.24 mmol) and the mixture was stirred for 16 h. The reaction was quenched by adding water and then extracted twice with $Et_2O$. The collected organic phases were washed with dilute HCl and brine and finally dried using $MgSO_4$. The crude product was purified by flash chromatography (FC) on silica using mixtures of $Et_2O$ and pentane as the eluent.

### 2-Nitro-1-phenylbutyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5a)

Prepared according to the general procedure at room temperature using nitronate **1a** (42 μL, 0.3 mmol) and benzaldehyde **2a** (22 μL, 0.2 mmol) as the starting material. As determined by $^1$H NMR the *threo : erythro* ratio was 5 : 1. The diastereomeric excess of *threo*-**5a** was 65% de as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 10 : 90 as the eluent which gave *threo*-**5a** in 76% yield (62.2 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.39–7.08 (m, 10H), 6.24 (d, $J$ = 10.4 Hz, 1H, 1 diastereomer), 6.14 (d, $J$ = 10.4 Hz, 1H, 2 diastereomer), 4.78–4.67 (m, 1H), 3.39 (s, 3H, 1 diastereomer), 3.28 (s, 3H, 2 diastereomer), 1.76–1.61 (m, 2H), 0.82–0.78 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 164.95, 134.96, 133.31, 130.11, 129.97, 129.90, 129.82, 129.62, 129.51, 128.99, 128.92, 128.46, 128.36, 127.95, 127.91, 127.47, 127.24, 127.16, 126.91, 125.51, 124.45, 91.39, 91.26, 78.40, 77.87, 55.70, 55.43, 23.79, 23.76, 9.80, 9.77; MS (TOF ES+): *m*/*z* 434 (M + Na)+; HRMS calc. for $C_{20}H_{20}F_3NO_5Na$ 434.1191; found 434.1188.

### 1-(4-Methoxyphenyl)-2-nitrobutyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5b)

Prepared according to the general procedure using nitronate **1a** (42 μL, 0.3 mmol) and *p*-methoxybenzaldehyde **2b** (31.2 mg, 0.2 mmol) as the starting material. The reaction was initiated at −78 °C and allowed to warm to room temperature over 16 h. As determined by $^1$H NMR the *threo : erythro* ratio was 3 : 1. The diastereomeric excess of *threo*-**5c** was 59% de as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 10 : 90 as the eluent which gave *threo*-**5b** in 34% yield (31.2 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.38–7.25 (m, 5H), 7.12 (d, $J$ = 9.3 Hz, 2H, 1. diastereomer), 7.08 (d, $J$ = 9.3 Hz, 2H, 2 diastereomers), 6.86 (d, J = 9.3 Hz, 2H, 1. diastereomer), 6.78 (d, $J$ = 9.3 Hz, 2H, 2 diastereomers), 6.22 (d, $J$ = 13.9 Hz, 1H, 1. diastereomer), 6.08 (d, $J$ = 13.9 Hz, 1H, 2 diastereomers), 4.78–4.64 (m, 1H), 3.96 (s, 3H, 2 diastereomers), 3.59 (s, 3H, 1 diastereomer), 3.28 (s, 3H, 2 diastereomers), 2.96 (s, 3H, 1 diastereomer), 1.77–1.64 (m, 2H, 2 diastereomers), 1.43–1.34 (m, 2H, 1. diastereomer), 0.95–0.86 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.86, 160.72, 160.60, 160.01, 135.98, 135.10, 130.89, 130.11, 129.78, 129.47, 129.40, 129.37, 129.27, 128.92, 128.21, 128.04, 114.95, 114.54, 114.29, 113.87, 91.97, 91.43, 91.29, 90.76, 78.54, 78.17, 56.12, 55.58, 55.34, 55.01, 23.83, 23.43, 10.21, 9.80; MS (TOF ES$^+$): *m*/*z* 464 (M + Na)$^+$; HRMS calc. for $C_{21}H_{22}F_3NO_6Na$ 464.1297; found 464.1298.

### 1-(4-Cyanophenyl)-2-nitrobutyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5c)

Prepared according to the general procedure using nitronate **1a** (42 μL, 0.3 mmol) and *p*-cyanobenzaldehyde **2c** (26.2 μL, 0.2 mmol) as the starting material. The reaction was initiated at −78 °C and allowed to warm to room temperature over 16 h. As determined by $^1$H NMR the *threo : erythro* ratio was >10 : 1. The diastereomeric excess of *threo*-**5c** was 40% as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 30 : 70 as the eluent which gave *threo*-**5c** in 47% yield (41.3 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.49–7.25 (m, 9H), 6.30 (d, $J$ = 10.6 Hz, 1H, 1 diastereomer), 6.21 (d, $J$ = 10.6 Hz, 1H, 2 diastereomers), 4.78–4.70 (m, 1H), 3.45 (s, 3H, 1 diastereomer), 3.34 (s, 3H, 2 diastereomers), 1.83–1.77 (m, 2H, 1 diastereomer), 1.42–1.37 (m, 2H, 2 diastereomers), 0.93–0.85 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 165.74, 165.13, 138.57, 138.29, 133.21, 132.64, 131.43, 130.15, 129.81, 129.34, 128.55, 128.13, 127.96,127.21, 126.75, 126.31, 117.70, 117.13, 114.92, 114.20, 114.03, 113.74, 110.00, 109.83, 90.74, 90.20, 78.94, 78.19, 56.39, 56,09, 23.60, 23.41, 10.06, 9.78; MS (TOF ES$^+$): *m*/*z* 459 (M+Na)$^+$; HRMS calc. for $C_{21}H_{19}F_3N_2O_5Na$ 459.1144, found 459.1130.

### 2-Nitro-1-(4-nitrophenyl)butyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5d)

Prepared according to the general procedure at room temperature using nitronate **1a** (42 μL, 0.3 mmol) and *p*-nitrobenzaldehyde **2d** (30.2 mg, 0.2 mmol) as the starting material. As determined by $^1$H NMR the *threo : erythro* ratio was >10 : 1. The diastereomeric excess of *threo*-**5d** was 50% as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 20 : 80 as the eluent which gave *threo*-**5d** in 63% yield (57.6 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.58–7.51 (m, 4H), 7.37–7.24 (m, 5H), 6.29 (d, $J$ = 11.1 Hz, 1H, 2 diastereomers), 6.21 (d, $J$ = 11.1 Hz, 1H, 1. diastereomer), 4.76–4.62 (m, 1H), 3.38 (s, 3H, 1 diastereomer), 3.26 (s, 3H, 2 diastereomers), 1.81–1.72 (m, 2H, 1 diastereomer), 1.36–1.29 (m, 2H, 2 diastereomers), 0.89–0.82 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 164.94, 164.32, 151.07, 150.78, 148.70, 148.23, 134.94, 134.21, 130.92, 130.47, 130.09, 129.83, 129.19, 128.72,

128.41, 128.15, 126.72, 126.05, 124.29, 123.86, 121.24, 121.03, 90.77, 90.23, 75.91, 75.25, 55.77, 55.21, 24.08, 23.60, 10.02, 9.76; MS (TOF ES$^+$): *m/z* 479 (M+Na)$^+$; HRMS calc. for $C_{20}H_{19}F_3N_2O_7Na$ 479.1042, found 479.1050.

**2-Nitro-1-(3-nitrophenyl)butyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5e)**

Prepared according to the general procedure at room temperature using nitronate **1a** (42 μL, 0.3 mmol) and *m*-nitrobenzaldehyde **2e** (30.2 mg, 0.2 mmol) as the starting material. As determined by $^1$H NMR the *threo : erythro* ratio was >10 : 1. The diastereomeric excess of *threo*-**5e** was 45% as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 15 : 85 as the eluent which gave *threo*-**5e** in 67% yield (61.1 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.51–7.04 (m, 9H), 6.38 (d, $J$ = 11.1 Hz, 1H, 1 diastereomer), 6.32 (d, $J$ = 11.1 Hz, 1H, 2 diastereomers), 4.78–4.64 (m, 1H), 3.41 (s, 3H, 1 diastereomer), 3.29 (s, 3H, 2 diastereomers), 2.19–2.09 (m, 2H, 1 diastereomer), 1.88–1.75 (m, 2H, 2 diastereomers), 0.86–0.81 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 163.46, 149.02, 148.72, 148.43, 158.13, 137.33, 136.84, 134.62, 134.28, 130.74, 130.37, 130.04, 129.78, 128.59, 128.03, 128.33, 127.93, 126.57, 166.21, 124.78, 124.49, 124.38, 124.01, 122.50, 122.12, 90.78, 90.41, 74.91, 74.03, 55.85, 55.32, 24.03, 23.63, 10.24, 9.75; MS (TOF ES$^+$): *m/z* 479 (M + Na)$^+$; HRMS calc. for $C_{20}H_{19}F_3N_2O_7Na$ 479.1042, found 479.1044.

**1-(2-Naphthyl)-2-nitrobutyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5f)**

Prepared according to the general procedure using nitronate **1a** (42 μL, 0.3 mmol) and 2-naphthaldehyde **2d** (42 μL, 0.2 mmol) as the starting material. The reaction was initiated at −78 °C and allowed to warm to room temperature over 16 h. As determined by $^1$H NMR the *threo : erythro* ratio was 2.5 : 1. The diastereomeric excess of *threo*-**5c** was 60% as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 10 : 90 as the eluent which gave *threo*-**5f** in 34% yield (31.2 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.82–7.61 (m, 4H), 7.47–7.20 (m, 8H), 6.41 (d, $J$ = 12.4 Hz, 1H, 1 diastereomer), 6.30 (d, $J$ = 12.4 Hz, 1H, 2 diastereomers), 4.88–4.74 (m, 1H), 3.41 (s, 3H, 1 diastereomer), 3.28 (s, 3H, 2 diastereomers), 1.83–1.72 (m, 2H, 1 diastereomer), 1.21–1.04 (m, 2H, 2 diastereomers), 0.84–0.79 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 173.72, 173.39, 136.42, 136.02, 134.62, 134.06, 132.60, 132.17, 129.51, 129.49, 129.12, 129.09, 128.85, 128.43, 128.38, 128.25, 128.21, 128.06, 127.98, 127.76, 127.67, 127.51, 127.46, 127.24, 127.21, 127.08, 126.85, 126.53, 124.17, 123.92, 122.71, 122.35, 102.31, 101.94, 91.49, 91.16, 78.88, 78.56, 49.65, 49.21, 24.06, 23.84, 10.13, 9.82; MS (TOF ES$^+$): *m/z* 484 (M + Na)$^+$; HRMS calc. for $C_{24}H_{22}F_3NO_5Na$ 484.1348, found 484.1349.

**2-Nitro-1-phenylheptyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5g)**

Prepared according to the general procedure using nitronate **1b** (61 mg, 0.3 mmol) and benzaldehyde **2a** (22 μL, 0.2 mmol) as the starting material. The reaction was initiated at −78 °C and allowed to warm to room temperature over 16 h. As determined by $^1$H NMR the *threo : erythro* ratio was 3 : 1. The diastereomeric excess of *threo*-**5g** was 43% as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 30 : 70 as the eluent which gave *threo*-**5g** in 81% yield (74.6 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.59–7.19 (m, 10H), 6.22 (d, $J$ = 12.2 Hz, 1H, 1 diastereomer), 6.12 (d, $J$ = 12.2 Hz, 1H, 2 diastereomers), 4.81–4.72 (m, 1H), 3.39 (s, 3H, 1diastereomer), 3.36 (s, 3H, 2 diastereomers), 1.78–1.71 (m, 2H, 1 diastereomer), 1.61–1.53 (m, 2H, 2 diastereomers), 1.32–1.21 (m, 6H), 0.77–0.69 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 164.94, 133.32, 133.23, 130.09, 130.05, 129.89, 29.83, 129.60, 129.49, 128.98, 128.90, 128.34, 128.21, 127.48, 127.31, 126.90, 126.81, 124.45, 121.57, 104.73, 90.01, 89.88, 78.59, 78.05, 75.72, 75.37, 31.52, 31.00, 25.84, 25.44, 24.93, 24.86, 22.28, 22.25, 13.82, 13.79; MS (TOF ES$^+$): *m/z* 476 (M+Na)$^+$; HRMS calc. for $C_{23}H_{26}F_3NO_5Na$ 476.1661, found 476.1656.

**2-Nitro-1-(2-phenylethenyl)butyl 2-trifluoromethyl-2-methoxy-2-phenylethanoate (5h)**

Prepared according to the general procedure using nitronate **1a** (42 mg, 0.3 mmol) and (*E*)-cinnamaldehyde **2g** (22 μL, 0.2 mmol) as the starting material. The reaction was initiated at −78 °C and allowed to warm to room temperature over 16 h. As determined by $^1$H NMR the *threo : erythro* ratio was >10 : 1. The diastereomeric excess of *threo*-**5h** was 45% as determined by $^{19}$F NMR of the crude product. FC was performed using $Et_2O$–pentane 10 : 90 as the eluent which gave *threo*-**5h** in 44% yield (38.6 mg). $^1$H NMR ($CDCl_3$) $\delta$ 7.36–7.23 (m, 10H), 6.75 (d, $J$ = 13.8 Hz, 1H, 2 diastereomers), 6.68 (d, $J$ = 13.8 Hz, 1H, 1 diastereomer), 6.02–5.94 (m, 1H), 5.83–78 (m, 1H), 4.43–4.54 (m, 1H), 2.03–1.78 (m, 2H), 3.42 (s, 3H, 1 diastereomer), 3.31 (s, 3H, 2 diastereomers), 0.98–0.91 (m, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 139.15, 138.83, 129.87, 129.62, 129.52, 129.24, 128.97, 128.84, 128.80, 128.43, 128.36, 127.89, 127.65, 127.54, 127.35, 127.04, 126.99, 126.94, 126.78, 121.60, 121.29, 119.21, 118.93, 90.46, 90.10, 76.34, 76.01, 53.92, 53.28, 23.94, 23.14, 10.23, 9.83; MS (TOF ES$^+$): *m/z* 460 (M+Na)$^+$; HRMS calc. for $C_{22}H_{22}F_3NO_5Na$ 460.1348, found 460.1356.

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