# Deactivation of Secondary Amine Catalysts via Aldol Reaction Amine Catalysis Under Solvent-Free Conditions 

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## Supporting Information

## Contents

1. General Aspects and Materials ............................................................................................. S2
2. In-situ MS Analysis of the Conjugate Addition Reaction Catalyzed by $\mathbf{1}$.................................. S3
3. Analytical Data of the Conjugate Addition Reaction Products $\mathbf{2 a} \mathbf{- 2 \mathbf { j }}$........................................ S7
4. ${ }^{1}$ H-NMR Spectra of $\gamma$-nitroaldehydes $\mathbf{2 a}-\mathbf{2 j}$.......................................................................... S14
5. References......................................................................................................................... S19

## 1. General Aspects and Materials

Reagents and materials were of the highest commercially available grade and used without further purification. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F254 aluminium sheets. Visualization of the compounds was achieved by UVVis or $\mathrm{KMnO}_{4}$. Flash chromatography and plug filtrations were performed using silica gel 60 (particle size $0.040-0.063 \mathrm{~mm}, 200-400$ mesh) manufactured by Fluka. Solvents for extraction and chromatography were of technical quality and distilled before use. ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra were recorded on a Bruker DRX 400, a Bruker AV III 400 ( $400 \mathrm{MHz} / 100 \mathrm{MHz}$ ) or a Bruker AV III $600(600 \mathrm{MHz} / 150 \mathrm{MHz}$ ). All spectra were recorded at $25^{\circ} \mathrm{C}$, unless stated otherwise. Chemical shifts ( $\delta$ ) are reported in parts per million ( ppm ) relative to the signal of tetramethylsilane (TMS) using the residual solvent signals. SFC analyses were performed on an analytical SFC with a diode array detector ACQUITY-UPLCPDA from Waters using chiral stationary phase columns (Trefoil, AS, AD, IA, Whelk, IC, OD, OJ) ( $150 \mathrm{~mm} \times 30 \mathrm{~mm}$ ) from Daicel or Waters under the reported conditions. HPLC analyses were performed on an analytical Ultimate 3000 HPLC system from Dionex with a diode array detector and chiral stationary phase columns (Daicel AD-H, Daicel AS-H, AY-H, OD-H or Daicel OJ-H). High-resolution electron ionization (HR-EI) mass spectra were measured on a Waters Micromass AutoSpec Ultima spectrometer. High-resolution MALDI spectra were acquired on a Bruker solariX 94 (ESI/MALDI-FT-ICR) and a Bruker UltraFlex II (MALDI-TOF) spectrometer. In-situ FT-IR spectroscopy was carried out on a ReactIR R4000 (SiComb probe) with a spectral range of $4000-650 \mathrm{~cm}^{-1}$. All measurements were performed at room temperature and spectra were recorded every minute. The peptidic catalysts $\mathbf{1}$ and $\mathbf{1 a}$ were prepared according to literature procedures. ${ }^{1,2}$

## 2. In-situ MS Analysis of the Conjugate Addition Reaction Catalyzed by $\mathbf{1}$

The TFA salt of $1(1 \mathrm{~mol} \%, 0.01 \mathrm{mmol}, 4.5 \mathrm{mg})$ and $(E)$-nitrostyrene ( 1.0 equiv., 1.0 mmol , 149.2 mg ) were dissolved in $\mathrm{CHCl}_{3} / \mathrm{PrOH} 9: 1(2 \mathrm{~mL})$. N-methyl morpholine ( $1 \mathrm{~mol} \%$, $0.01 \mathrm{mmol}, 1.1 \mu \mathrm{~L}$ ) and butanal ( 1.5 equiv., $1.0 \mathrm{mmol}, 135.6 \mu \mathrm{~L}$ ) were added and the reaction mixture was stirred for 1 h . The reaction mixture was diluted with MeOH and analyzed by mass spectrometry (ESI+).

Mass spectrum:


Peaks with the mass corresponding to the following structures were identified:
$\gamma$-nitroaldehyde 2a $\left([\mathrm{M}+\mathrm{Na}]^{+}=\mathbf{2 4 4 . 0 9 4 7} \mathbf{~ m} / \mathrm{z}\right)$ :


Intens.

Peptide $1\left([\mathrm{M}+\mathrm{Na}]^{+}=\mathbf{3 6 3 . 1 6 4 2} \mathbf{~ m} / \mathrm{z}\right)$ :



Peptide iminium (left) ([M] $]^{+}$) and/or enamine intermediate $\left([M+H]^{+}\right)(395.2290 \mathrm{~m} / \mathrm{z}):$



Peptide 1 and $\beta$-hydroxyaldehyde condensate $4\left([M]^{+} /[\mathrm{M}+\mathrm{H}]^{+}=467.2858 \mathrm{~m} / \mathrm{z}\right)$ :




Note: The MS analysis was performed after diluting the sample that contained $1 \mathrm{~mol} \%$ of the peptidic catalyst by $100-1000$ fold with MeOH , conditions that were necessary for the MS analysis that do, however, also favor hydrolysis of enamines. The signal intensity of enamines 1-En and $\mathbf{4}$ is therefore low.

Peptide condensate with product 2a $\left([M]^{+}=\mathbf{5 4 4 . 2 7 6 1} \mathbf{~ m} / \mathrm{z}\right)$ :



Note: Related compounds (e.g., enamine, cyclobutane, nitronate, dihydrooxazine-N-oxide) have the same mass and could therefore not be distinguished.

## 3. Analytical Data of the Conjugate Addition Reaction Products 2a-2j

## (2S,3R)-2-Ethyl-4-nitro-3-phenylbutanal 2a


diastereomeric ratio: 61:1


enantiomeric excess: $97 \%$


## Crystal Structure of 2a:


(Ellipsoid contour: 50\% probability)

| Identification code | w360817_1_1 |
| :---: | :---: |
| Empirical formula | $\mathrm{C}_{12} \mathrm{H}_{15} \mathrm{NO}_{3}$ |
| Formula weight | 221.25 |
| Temperature/K | 100.0(1) |
| Crystal system | orthorhombic |
| Space group | $\mathrm{P} 2{ }_{12} 2_{1}$ |
| a/Å | 5.47770(10) |
| b/Å | 8.3194(2) |
| c/Å | 25.6879(5) |
| $\alpha /{ }^{\circ}$ | 90 |
| $\beta /{ }^{\circ}$ | 90 |
| $\gamma{ }^{\circ}$ | 90 |
| Volume/ $\AA^{3}$ | 1170.63(4) |
| Z | 4 |
| $\rho_{\text {calcg }} / \mathrm{cm}^{3}$ | 1.255 |
| $\mu / \mathrm{mm}^{-1}$ | 0.743 |
| F(000) | 472.0 |
| Crystal size/ $/ \mathrm{mm}^{3}$ | $0.146 \times 0.089 \times 0.08$ |
| Radiation | $\mathrm{CuK} \alpha(\lambda=1.54184)$ |
| $2 \Theta$ range for data collection $/{ }^{\circ} 6.882$ to 133.058 |  |
| Index ranges | $-6 \leq \mathrm{h} \leq 5,-8 \leq \mathrm{k} \leq 9,-30 \leq 1 \leq 28$ |
| Reflections collected | 6939 |
| Independent reflections | 1953 [ $\left.\mathrm{R}_{\text {int }}=0.0396, \mathrm{R}_{\text {sigma }}=0.0334\right]$ |
| Data/restraints/parameters | 1953/0/146 |
| Goodness-of-fit on $\mathrm{F}^{2}$ | 1.077 |
| Final R indexes [ $\mathrm{I}>=2 \sigma$ ( I ] | $\mathrm{R}_{1}=0.0335, \mathrm{wR}_{2}=0.0834$ |
| Final R indexes [all data] | $\mathrm{R}_{1}=0.0352, \mathrm{wR}_{2}=0.0844$ |
| Largest diff. peak/hole / e $\AA^{-3} 0.12 /-0.19$ |  |
| Flack parameter | 0.08(17) |

A suitable crystal was selected and measured on a XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer. The crystal was kept at $100.0(1) \mathrm{K}$ during data collection. Using Olex2, ${ }^{4}$ the structure was solved with the ShelXT ${ }^{5}$ structure solution program using Intrinsic Phasing and refined with the ShelXL ${ }^{6}$ refinement package using Least Squares minimization.

The crystal structure is deposited in the Cambridge Crystallographic Data Centre (CCDC Code: 1967754).

## (2S,3R)-2-Methyl-4-nitro-3-phenylbutanal 2b



Yield $=96 \%, 21: 1$ d.r., $98 \% \mathrm{ee}$. The analytical data are in agreement with previously published data. ${ }^{1}$

The reference HPLC chromatogram of the racemic sample was reported in ref. 6.
diastereomeric ratio: 21:1

enantiomeric excess: $98 \%$


## (S)-2-((R)-2-Nitro-1-phenylethyl)hexanal 2c



Yield $=>95 \%, 60: 1$ d.r., $98 \% e e$. The analytical data are in agreement with previously published data. ${ }^{1}$

The reference HPLC chromatogram of the racemic sample was reported in ref. 1 .
diastereomeric ratio: 60:1

enantiomeric excess: 98\%


## (S)-2-((R)-2-Nitro-1-phenylethyl)pentanal 2d


diastereomeric ratio: 33:1


## (2S,3R)-2-Isopropyl-4-nitro-3-phenylbutanal 2e



The reference HPLC chromatogram of the racemic sample was reported in ref. 7 .
diastereomeric ratio: 56:1

enantiomeric excess: $99 \%$


| No. | Ret.Time <br> min | Peak Name | Height <br> mAU | Area <br> mAU ${ }^{*}$ min | Rel.Area <br> $\%$ | Amount | Type |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 17.18 | n.a. | 0.521 | 0.161 | 0.37 | n.a. | BMB $^{*}$ |
| 2 | 20.58 | n.a. |  | 73.890 | 42.928 | 99.63 | n.a. |
| BMB $^{*}$ |  |  |  |  |  |  |  |
| Total: |  |  |  | 74.410 | 43.090 | 100.00 | 0.000 |

## (2S,3R)-2-Benzyl-4-nitro-3-phenylbutanal $2 f$



Yield $=>95 \%$, $37: 1$ d.r., $98 \% e e$. The analytical data are in agreement with previously published data. ${ }^{1}$

The reference HPLC chromatogram of the racemic sample was reported in ref. 1.
diastereomeric ratio: 37:1 enantiomeric excess: $98 \%$


## (2S,3S)-2-Ethyl-3-(furan-2-yl)-4-nitrobutanal 2g



Yield $=91 \%, 27: 1$ d.r., $98 \%$ ee ( 3 equivalents of butanal were used). The analytical data are in agreement with previously published data. ${ }^{10}$

The reference HPLC chromatogram of the racemic sample was reported in ref. 8 .
diastereomeric ratio: 27:1


enantiomeric excess: 98\%


## (2S,3R)-2-Ethyl-3-(4-methoxyphenyl)-4-nitrobutanal 2 h



Yield $=94 \%$, 41:1 d.r., $96 \%$ ee ( 3 equivalents of butanal were used, 3 days reaction time). The analytical data are in agreement with previously published data. ${ }^{1}$

The reference HPLC chromatogram of the racemic sample was reported in ref. 9 .
diastereomeric ratio: 41:1


enantiomeric excess: $96 \%$


## (2S,3R)-2-Ethyl-3-(4-fluorophenyl)-4-nitrobutanal 2i



Yield $=96 \%, 4: 1$ d.r., $95 \%$ ee ( $0.2 \mathrm{~mol} \% \mathbf{1 a}$ and NMM and 3 equivalents butanal was used). The analytical data are in agreement with previously published data. ${ }^{9}$

The reference HPLC chromatogram of the racemic sample was reported in ref. 10.
diastereomeric ratio: 41:1


enantiomeric excess: $95 \%$

(2S,3R)-3-(4-Chlorophenyl)-2-ethyl-4-nitrobutanal 2j


Yield $=96 \%, 46: 1$ d.r., $94 \%$ ee ( $0.2 \mathrm{~mol} \%$ 1a and NMM and 3 equivalents butanal was used). The analytical data are in agreement with previously published data. ${ }^{9}$

The reference HPLC chromatogram of the racemic sample was reported in ref. 10 .
diastereomeric ratio: 46:1

enantiomeric excess: $94 \%$


## 4. ${ }^{\mathbf{1}} \mathbf{H}$-NMR Spectra of $\gamma$-nitroaldehydes $\mathbf{2 a} \mathbf{a} \mathbf{2} \mathbf{j}$

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of $\mathbf{2 a}$

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of 2b




## ${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ of $\mathbf{2 c}$

## 



${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of 2d



${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of $\mathbf{2 e}$


${ }^{1} \mathrm{H}$ NMR $\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ of $\mathbf{2 f}$

${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of $\mathbf{2 g}$



${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of $\mathbf{2 h}$
致
${ }_{4}^{4}$


${ }^{1} \mathrm{H}$ NMR ( $400 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) of $\mathbf{2 i}$





${ }^{1} \mathrm{H} \mathrm{NMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right)$ of $\mathbf{2 j}$


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