Supporting Information

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Catalytic Asymmetric 1,3-Dipolar Cycloaddition
Reactions of Azomethine Ylides – A Simple Approach to Optically Active Highly Functionalized Proline Derivatives

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General Methods. All reactions were carried out using standard Schlenk techniques in a nitrogen atmosphere. The $^1$H NMR and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for $^1$H NMR and relative to the central CDCl$_3$ resonance ($\delta = 77.0$). Column chromatography was carried out using Merck silica gel 60 (230-400 mesh). Thin layer chromatography (TLC) was performed on Merck silica gel 60 F$_{254}$ plates and visualized by UV-light (254 nm) or by an aqueous mixture of KMnO$_4$, K$_2$CO$_3$ and NaOH. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The
enantiomeric excess (ee) of the products was determined by HPLC using Daicel Chiralpak AS or OJ columns with 2-propanol/hexane as eluent. HRMS spectra were recorded on a Micromass LC-TOF instrument. The relative stereochemistry of the products was found by comparison of the $^1$H NMR values with literature values.$^{[1,2]}$

**Materials.** The solvents used were dried/purified as follows: tetrahydrofuran (THF), Et$_2$O and toluene were distilled from sodium. Et$_3$N, CH$_2$Cl$_2$ and CH$_3$CN were distilled from CaH$_2$. Methyl acrylate was dried over activated molecular sieves (4Å). 2,2′-Isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline]$^{[3]}$ and 4,6-dibenzofurandiy1-2,2′-bis[4(R)-phenyl-1,3-oxazoline]$^{[4]}$ were prepared according to literature procedures. Cu(OTf)$_2$, Zn(OTf)$_2$, dimethyl fumarate, 2,2′-isopropylidenebis[(4R)-4-phenyl-2-oxazoline], 1-naphtthaldehyde, 2-naphtthaldehyde and p-bromobenzaldehyde were purchased from Aldrich and used as received. Benzaldehyde was distilled before use.

**Representative Procedure for the Preparation of the Imines.**$^{[5]}$

To a suspension of 5.78 g (46 mmol) glycine methyl ester hydrochloride in CH$_2$Cl$_2$ (70 mL) was added 10 g MgSO$_4$ and 7 mL (50 mmol) of Et$_3$N. The mixture was stirred for 1 h at room
temperature. Then the aldehyde (40 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was filtered and the organic phase was washed with H$_2$O (2 x 50 mL), dried over MgSO$_4$, filtered and evaporated. The imines showed satisfactory purity as determined by $^1$H NMR spectroscopy and were used without further purification.

**General Procedure for the Zn$^{II}$-Catalyzed 1,3-Dipolar Cycloaddition.** Zn(OTf)$_2$ (0.02 mmol) was placed in a pre-dried Schlenk tube and subjected to a vacuum while heated with a heating gun. The reaction flask was allowed to cool to rt and then refilled with N$_2$. The ligand, 2,2’-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] (0.023 mmol), was added and the mixture was stirred under vacuum for 0.5-1 h. The reaction flask was then refilled with N$_2$ and dry solvent was added (2 mL). After stirring for 1 h the reaction mixture was cooled to -20°C and the imine (0.2 mmol), Et$_3$N (0.02 mmol) and the alkene (0.22 mmol) were added. The reaction mixture was stirred overnight at -20°C and then warmed to room temperature. Evaporation of the solvent afforded the crude product, which was purified by column chromatography to give the proline derivatives.
(2S,4S,5R)-5-Phenylpyrrolidine-2,4-dicarboxylic acid dimethyl ester (4a) Purified by column chromatography using SiO$_2$ and 100% Et$_2$O to give a pale yellow oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (90:10); flow rate 1.0 mL/min, $\tau_{\text{major}}$ = 13.2 min; $\tau_{\text{minor}}$ = 21.2 min). Yield: 80%. $[\alpha]_{\text{D}}^\text{rt}$ = +38° (c = 0.10 g/100 mol, CH$_2$Cl$_2$, 88% ee). HRMS C$_{14}$H$_{17}$NO$_4$ [M+Na]$^+$ calculated 286.1056, found 286.1058. $^1$H NMR and $^{13}$C NMR were consistent with previously reported values.$^{[1]}$

(2S,4S,5R)-5-Naphthalen-2'-yl-pyrrolidine-2,4-dicarboxylic acid dimethyl ester (4b) Purified by column chromatography using SiO$_2$ and 100% Et$_2$O to give a colorless oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (90:10); flow rate 1.0 mL/min, $\tau_{\text{major}}$ = 12.9 min; $\tau_{\text{minor}}$ = 24.4 min). Yield: 84%. $[\alpha]_{\text{D}}^\text{rt}$ = +34° (c = 0.10 g/100 mL, CH$_2$Cl$_2$, 91% ee). HRMS C$_{14}$H$_{17}$NO$_4$ [M+Na]$^+$ calculated 336.1212, found 336.1208. $^1$H NMR was consistent with previously reported values.$^{[2]}$ $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$
(2S,4S,5R)-5-Naphthalen-2′-yl-pyrrolidine-2,4-dicarboxylic acid 4-ethyl ester 2-methyl ester (4c) The reaction was performed at room temperature. Purified by column chromatography using SiO₂ and 100% Et₂O to give a colorless oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (90:10); flow rate 1.0 mL/min, τ_major = 13.2 min; τ_minor = 25.8 min). Yield: 76%. [α]_D = +15° (c = 0.10 g/100 mL, CH₂Cl₂, 68% ee). HRMS C₁₄H₁₇NO₄ [M+Na]^+ calculated 350.1369, found 350.1366. ³¹H NMR (400 MHz, CDCl₃) δ 7.79 (m, 4H, ArH), 7.44 (m, 3H, ArH), 4.68 (d, J = 8.2 Hz, 1H, H-5), 4.04 (dd, J = 8.6 Hz, J = 7.8 Hz, 1H, H-2), 3.84 (s, 3H, CO₂CH₃), 3.52 (dq, J = 7.0 Hz, J = 10.9 Hz, 1H, OCH₂CH₃), 3.63 (dq, J = 7.0 Hz, J = 10.9 Hz, 1H, OCH₂CH₃), 3.38 (dt, J = 7.8 Hz, J = 6.2 Hz, 1H, H-4), 2.47 (m, 2H, H-3), 0.64 (t, J = 7.0 Hz, 3H, OCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 173.0, 136.6, 133.4, 133.1, 128.2, 128.0,
5-Naphthalen-2′-yl-pyrrolidine-2,4-dicarboxylic acid 4-tert-butyl ester 2-methyl ester (4d) The reaction was performed at room temperature and the crude mixture was purified by column chromatography using SiO\(_2\) and 100% Et\(_2\)O to give white powder, mp = 74-75 °C. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (85:15); flow rate 1.0 mL/min, \(\tau_{\text{major}} = 8.8\) min; \(\tau_{\text{minor}} = 13.5\) min). 3% ee, Yield: 12%. HRMS C\(_{14}\)H\(_{17}\)NO\(_4\) [M+Na]\(^+\) calculated 378.1682, found 378.1683. \(^1\)H NMR and \(^{13}\)C NMR were consistent with previously reported values.\(^{[1]}\)

(2S,4S,5R)-5-(4′-Bromophenyl)-pyrrolidine-2,4-dicarboxylic acid dimethyl ester (4e) Purified by column chromatography using SiO\(_2\) and 100% Et\(_2\)O to give colorless oil. The ee was determined by HPLC using Chiralpak AS column (hexane/2-propanol (80:20); flow rate 1.0 ml/min, \(\tau_{\text{major}} = 9.6\)
min; $\tau_{\text{minor}} = 19.9$ min). Yield: 89%. $[\alpha]^{\text{rt}}_D = +34^\circ$ (c = 0.19 g/100 mL, CH$_2$Cl$_2$, 94% ee). HRMS C$_{14}$H$_{17}$NO$_4$ [M+Na]$^+$ calculated 364.0161, found 364.0159. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 (d, $J$ = 8.4 Hz, 2H, ArH), 7.16 (d, $J$ = 8.4 Hz, 2H, ArH), 4.44 (d, $J$ = 7.4 Hz, 1H, H-5), 3.91 (t, $J$ = 8.2 Hz, 1H, H-2), 3.76 (s, 3H, CO$_2$CH$_3$), 3.24 (q, $J$ = 7.4 Hz, 1H, H-4), 3.20 (s, 3H, CO$_2$CH$_3$), 2.69 (bs, 1H, NH), 2.35 (dd, $J$ = 8.2 Hz, $J$ = 7.4 Hz, 2H, H-3); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.7, 172.7, 138.3, 131.2, 128.5, 121.4, 64.9, 59.7, 52.3, 51.4, 49.4, 33.0.

(2S,3S,4S,5R)-5-Phenylpyrrolidine-2,3,4-tricarboxylic acid trimethyl ester (4f) Purified by column chromatography using SiO$_2$ and 10% Et$_2$O in CH$_2$Cl$_2$ to give a colorless oil. The ee was determined by HPLC using a Chiralpak OJ column (hexane/2-propanol (70:30); flow rate 1.0 mL/min, $\tau_{\text{major}} = 18.0$ min; $\tau_{\text{minor}} = 26.7$ min). Yield: 78%. $[\alpha]^{\text{rt}}_D = +20^\circ$ (c = 0.35 g/100 mL, CH$_2$Cl$_2$, 76% ee). HRMS C$_{14}$H$_{17}$NO$_4$ [M+Na]$^+$ calculated 344.1110, found 344.1107. $^1$H NMR and $^{13}$C NMR were consistent with previously reported values.$^{[1]}$
(2S,3S,4S,5R)-5-Naphthalen-2'-yl-pyrrolidine-2,3,4-tricarboxylic acid trimethyl ester (4g) Purified by column chromatography using SiO₂ and 10% Et₂O in CH₂Cl₂ to give a colorless oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (90:10); flow rate 1.0 mL/min, \( \tau_{\text{major}} = 26.7 \text{ min} \); \( \tau_{\text{minor}} = 31.7 \text{ min} \)). Yield: 84%. \([\alpha]^{\text{rt}}_D = +10^\circ \) (c = 0.215 g/100 mL, CH₂Cl₂, 90% ee). HRMS C₁₄H₁₇NO₄ [M+Na]\(^+\) calculated 394.1267, found 394.1266. \(^1\)H NMR was consistent with previously reported values.\(^2\) \(^{13}\)C NMR (100 MHz, CDCl₃) δ 172.9, 172.3, 172.0, 135.7, 133.3, 133.2, 128.1, 127.8, 126.4, 126.3, 125.8, 125.2, 65.8, 63.6, 53.9, 52.9, 52.9, 51.9, 51.0.

(2S,3S,4S,5R)-5-(4'-Bromo-phenyl)-pyrrolidine-2,3,4-tricarboxylic acid trimethyl ester (4h) Purified by column chromatography using SiO₂ and 10% Et₂O in CH₂Cl₂ to give a colorless oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (95:5); flow rate 1.0 mL/min, \( \tau_{\text{major}} = 33.7 \text{ min} \); \( \tau_{\text{minor}} = 39.7 \text{ min} \)). Yield: 87%. \([\alpha]^{\text{rt}}_D = \)
$+12^\circ$ (c = 0.26 g/100 mL, CH$_2$Cl$_2$, 68% ee). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 (d, $J = 8.4$ Hz, 2H, ArH), 7.20 (d, $J = 8.4$ Hz, 2H, ArH), 4.61 (t, $J = 8.1$ Hz, $J = 8.1$ Hz, 1H, H-5), 4.19 (dd, $J = 7.3$ Hz, $J = 8.1$ Hz, 1H, H-2), 3.83 (s, 3H, CO$_2$CH$_3$), 3.76 (s, 3H, CO$_2$H$_3$), 3.64 (dd, $J = 5.7$ Hz, $J = 7.3$ Hz, 1H, H-3), 3.55 (dd, $J = 5.7$ Hz, $J = 8.1$ Hz, 1H, H-4), 2.75 (t, $J = 8.1$ Hz, $J = 8.1$ Hz, 1H, NH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.5, 171.9, 171.4, 137.3, 131.4, 128.6, 121.8, 64.6, 63.1, 53.4, 52.7, 52.6, 51.8, 50.3.

![Chemical structure](image)

(2S,3S,4S,5R)-5-Naphthalen-2′-yl-1-(toluene-4-sulfonyl)-pyrrolidine-2,3,4-tricarboxylic acid trimethyl ester (6) Compound 4g and p-toluenesulfonyl chloride was dissolved in CH$_2$Cl$_2$. Triethyleamine was added and the mixture was refluxed for 20 hr. The solvent was evaporated and the crude product was purified by column chromatography using SiO$_2$. The excess p-toluenesulfonyl chloride was eluted with CH$_2$Cl$_2$ after which the product was eluted with Et$_2$O to give a quantitative yield. Recrystallisation in a mixture of EtOAc and pentane afforded crystals suitable for X-ray analysis, mp = 107-8 °C. The ee was determined by HPLC using a Chiralpak OD
column (hexane/2-propanol (90:10); flow rate 1.0 mL/min, 
\( \tau_{\text{major}} = 11.8 \text{ min} \); \( \tau_{\text{minor}} = 16.1 \text{ min} \). \([\alpha]_{D}^{c} = +89.6^\circ \) (c = 0.115 g/100 mL, CH\(_2\)Cl\(_2\), 94.5% ee). HRMS C\(_{27}\)H\(_{27}\)NO\(_8\)S [M+Na]\(^+\) calculated 548.1355, found 548.1360. \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.79 (s, 1H, ArH), 7.68 (m, 2H, ArH), 7.60 (d, 1H, \( J = 8.5 \text{ Hz} \), ArH), 7.51 (d, 2H, \( J = 8.0 \text{ Hz} \), ArH), 7.38 (m, 3H, ArH), 6.99 (d, 2H, \( J = 8.0 \text{ Hz} \), ArH), 5.33 (d, 1H, \( J = 9.4 \text{ Hz} \), H-5), 4.49 (d, 1H, \( J = 9.4 \text{ Hz} \), H-2), 3.86 (s, 3H, CO\(_2\)CH\(_3\) ), 3.84 (dd, 1H, \( J = 9.4 \text{ Hz} \), \( J = 10.9 \text{ Hz} \), H-3), 3.66 (s, 3H, CO\(_2\)CH\(_3\) ), 3.59 (dd, 1H, \( J = 9.4 \text{ Hz} \), \( J = 10.9 \text{ Hz} \), H-4), 3.15 (s, 3H, CO\(_2\)CH\(_3\) ), 2.16 (s, 3H, ArCH\(_3\) ) \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 171.1, 170.1, 168.5, 144.4, 134.8, 134.5, 133.2, 133.1, 129.6, 128.4, 128.2, 128.1, 127.7, 127.4, 126.24, 126.17, 125.2, 64.6, 63.5, 53.3, 53.2, 52.23, 52.21, 48.1, 21.6.

X-ray work: Crystals of 6 are monoclinic, space group P2\(_1\), with unit cell at 120K: a = 9.7747(8)\(\text{Å} \), b = 11.8018(9)\(\text{Å} \), c = 10.4781(8)\(\text{Å} \), \( \beta = 90.132(2) \text{°} \), V = 1208.7(2)\(\text{Å}^3 \), Z = 2, \( \rho_{\text{calc}} = 1.444 \), \( \mu = 1.88\text{cm}^{-1} \) (MoK\(\alpha \) radiation, \( \lambda = 0.71073\text{Å} \)), \( F(000) = 552 \), \( T = 120\text{K} \).

16861 reflections collected on a SMART diffractometer, 6855 independent, 4712 significant (I > 3\(\sigma(I) \)). Structure solved by means of the SIR97 program system.\(^[6]\) Least squares refinement according to Rogers\(^[7]\) included a parameter which
is supposed to be 1.0 if the chirality is correct, -1.0 if it is wrong; the result is 1.01(15). The 4712 reflections used included 2029 Bijvoet pairs, 443 parameters were refined, final R = 0.044, R_w = 0.046. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-188992. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
Table 1. Effect of solvent in the reaction of \(N\text{-}2\text{-}naphthylidene\) glycinate (\(1b\)) and methyl acrylate (\(3a\)) in the presence of \(\text{Zn(OTf)}_2\) and ligand \(5a\).

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<th>Entry(^a)</th>
<th>Solvent</th>
<th>Ee  (%)</th>
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<td>1</td>
<td>Toluene</td>
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</tr>
<tr>
<td>2</td>
<td>(\text{Et}_2\text{O})</td>
<td>24.5</td>
</tr>
<tr>
<td>3</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
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<td>MeCN</td>
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</tr>
<tr>
<td>6</td>
<td>(3a)</td>
<td>76</td>
</tr>
</tbody>
</table>

\(a\): \(\text{Zn(OTf)}_2\), ligand \(5a\) and \(\text{Et}_3\text{N}\) were used in 10 mol\%. 

Table 2. Effect of the amount of base in the Zn$^{II}$-catalyzed reaction of $N$-2-naphthylidene glycinate ($1b$) and methyl acrylate ($3a$).

<table>
<thead>
<tr>
<th>Entry$^a$</th>
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<th>Ee (%)</th>
</tr>
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<td>6</td>
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$^a$: Zn(OTf)$_2$ and ligand $5a$ was used in 10 mol%.
REFERENCES


