



## 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  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to TMS ( $\delta = 0$ ) for  $^1\text{H}$  NMR and relative to the central  $\text{CDCl}_3$  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  $\text{F}_{254}$  plates and visualized by UV-light (254 nm) or by an aqueous mixture of  $\text{KMnO}_4$ ,  $\text{K}_2\text{CO}_3$  and  $\text{NaOH}$ . 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  $^1\text{H}$  NMR values with literature values.<sup>[1,2]</sup>

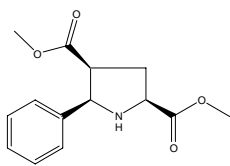
**Materials.** The solvents used were dried/purified as follows: tetrahydrofuran (THF),  $\text{Et}_2\text{O}$  and toluene were distilled from sodium.  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$  and  $\text{CH}_3\text{CN}$  were distilled from  $\text{CaH}_2$ . Methyl acrylate was dried over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

**Representative Procedure for the Preparation of the Imines.**<sup>[5]</sup>

To a suspension of 5.78 g (46 mmol) glycine methyl ester hydrochloride in  $\text{CH}_2\text{Cl}_2$  (70 mL) was added 10 g  $\text{MgSO}_4$  and 7 mL (50 mmol) of  $\text{Et}_3\text{N}$ . The mixture was stirred for 1 h at room

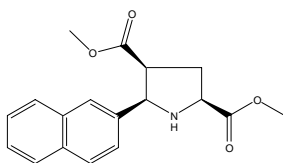
temperature. Then the aldehyde (40 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was filtered and the organic phase was washed with H<sub>2</sub>O (2 x 50 mL), dried over MgSO<sub>4</sub>, filtered and evaporated. The imines showed satisfactory purity as determined by <sup>1</sup>H NMR spectroscopy and were used without further purification.

**General Procedure for the Zn<sup>II</sup>-Catalyzed 1,3-Dipolar Cycloaddition.** Zn(OTf)<sub>2</sub> (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<sub>2</sub>. The ligand, 2,2'-isopropylidenebis[(4*S*)-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<sub>2</sub> 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<sub>3</sub>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.



**(2*S*,4*S*,5*R*)-5-Phenylpyrrolidine-2,4-dicarboxylic**

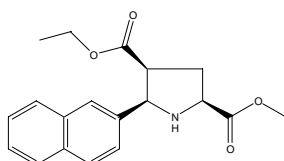
**acid dimethyl ester (4a)** Purified by column chromatography using SiO<sub>2</sub> and 100% Et<sub>2</sub>O to give a pale yellow oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (90:10); flow rate 1.0 mL/min,  $\tau_{\text{major}}$  = 13.2 min;  $\tau_{\text{minor}}$  = 21.2 min). Yield: 80%.  $[\alpha]_{\text{D}}^{\text{rt}}$  = +38° (c = 0.10 g/100 mol, CH<sub>2</sub>Cl<sub>2</sub>, 88% ee). HRMS C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> calculated 286.1056, found 286.1058. <sup>1</sup>H NMR and <sup>13</sup>C NMR were consistent with previously reported values.<sup>[1]</sup>



**(2*S*,4*S*,5*R*)-5-Naphthalen-2'-yl-pyrrolidine-2,4-**

**dicarboxylic acid dimethyl ester (4b)** Purified by column chromatography using SiO<sub>2</sub> and 100% Et<sub>2</sub>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<sub>2</sub>Cl<sub>2</sub>, 91% ee). HRMS C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> calculated 336.1212, found 336.1208. <sup>1</sup>H NMR was consistent with previously reported values.<sup>[2]</sup> <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$

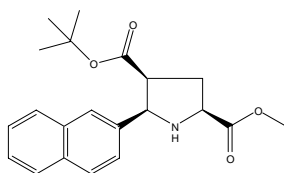
174.1, 173.4, 136.7, 133.4, 133.1, 128.3, 128.0, 127.8, 126.3, 126.1, 125.6, 125.3, 66.3, 60.2, 52.6, 51.6, 49.8, 33.7.



**(2*S*,4*S*,5*R*)-5-Naphthalen-2'-yl-pyrrolidine-2,4-**

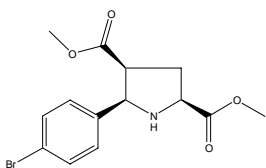
**dicarboxylic acid 4-ethyl ester 2-methyl ester (4c)** The reaction was performed at room temperature. Purified by column chromatography using SiO<sub>2</sub> and 100% Et<sub>2</sub>O to give a colorless oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (90:10); flow rate 1.0 mL/min,  $\tau_{\text{major}}$  = 13.2 min;  $\tau_{\text{minor}}$  = 25.8 min). Yield: 76%.  $[\alpha]_{\text{D}}^{\text{rt}}$  = +15° (c = 0.10 g/100 mL, CH<sub>2</sub>Cl<sub>2</sub>, 68% ee). HRMS C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> calculated 350.1369, found 350.1366. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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, CO<sub>2</sub>CH<sub>3</sub>), 3.52 (dq, *J* = 7.0 Hz, *J* = 10.9 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>), 3.63 (dq, *J* = 7.0 Hz, *J* = 10.9 Hz, 1H, OCH<sub>2</sub>CH<sub>3</sub>), 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, OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  174.0, 173.0, 136.6, 133.4, 133.1, 128.2, 128.0,

127.8, 126.3, 126.1, 125.6, 125.5, 66.3, 60.5, 60.2, 52.6, 49.8, 33.9, 13.8.



**5-Naphthalen-2'-yl-pyrrolidine-2,4-**

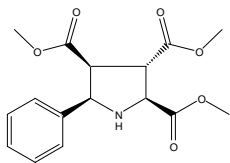
**dicarboxylic acid 4-tert-butyl ester 2-methyl ester (4d)** The reaction was performed at room temperature and the crude mixture was purified by column chromatography using SiO<sub>2</sub> and 100% Et<sub>2</sub>O to give white powder, mp = 74-75 °C. The ee was determined by HPLC using a Chiralpak AS 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<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> calculated 378.1682, found 378.1683. <sup>1</sup>H NMR and <sup>13</sup>C NMR were consistent with previously reported values.<sup>[1]</sup>



**(2S,4S,5R)-5-(4'-Bromophenyl)-pyrrolidine-2,4-**

**dicarboxylic acid dimethyl ester (4e)** Purified by column chromatography using SiO<sub>2</sub> and 100% Et<sub>2</sub>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

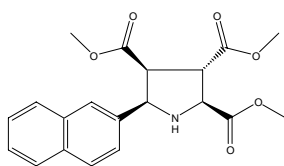
min;  $\tau_{\text{minor}} = 19.9$  min). Yield: 89%.  $[\alpha]_{\text{D}}^{\text{rt}} = +34^{\circ}$  ( $c = 0.19$  g/100 mL,  $\text{CH}_2\text{Cl}_2$ , 94% ee). HRMS  $\text{C}_{14}\text{H}_{17}\text{NO}_4$   $[\text{M}+\text{Na}]^+$  calculated 364.0161, found 364.0159.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  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,  $\text{CO}_2\text{CH}_3$ ), 3.24 (q,  $J = 7.4$  Hz, 1H, H-4), 3.20 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 2.69 (bs, 1H, NH), 2.35 (dd,  $J = 8.2$  Hz,  $J = 7.4$  Hz, 2H, H-3);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  173.7, 172.7, 138.3, 131.2, 128.5, 121.4, 64.9, 59.7, 52.3, 51.4, 49.4, 33.0.



**(2*S*,3*S*,4*S*,5*R*)-5-Phenylpyrrolidine-2,3,4-**

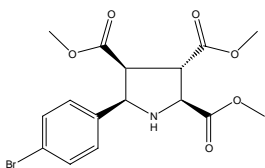
**tricarboxylic acid trimethyl ester (4f)** Purified by column chromatography using  $\text{SiO}_2$  and 10%  $\text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  to give a colorless oil. The ee was determined by HPLC using a Chiralpak OJ column (hexane/2-propanol (70:30); flow rate 1.0 mL/min,  $\tau_{\text{major}} = 18.0$  min;  $\tau_{\text{minor}} = 26.7$  min). Yield: 78%.  $[\alpha]_{\text{D}}^{\text{rt}} = +20^{\circ}$  ( $c = 0.35$  g/100 mL,  $\text{CH}_2\text{Cl}_2$ , 76% ee). HRMS  $\text{C}_{14}\text{H}_{17}\text{NO}_4$   $[\text{M}+\text{Na}]^+$  calculated 344.1110, found 344.1107.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR were consistent with previously reported values.<sup>[1]</sup>





**(2*S*,3*S*,4*S*,5*R*)-5-Naphthalen-2'-yl-pyrrolidine-**

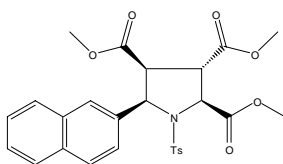
**2,3,4-tricarboxylic acid trimethyl ester (4g)** Purified by column chromatography using SiO<sub>2</sub> and 10% Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> to give a colorless oil. The ee was determined by HPLC using a Chiralpak AS column (hexane/2-propanol (90:10); flow rate 1.0 mL/min,  $\tau_{\text{major}}$  = 26.7 min;  $\tau_{\text{minor}}$  = 31.7 min). Yield: 84%.  $[\alpha]_{\text{D}}^{\text{rt}}$  = +10° (c = 0.215 g/100 mL, CH<sub>2</sub>Cl<sub>2</sub>, 90% ee). HRMS C<sub>14</sub>H<sub>17</sub>NO<sub>4</sub> [M+Na]<sup>+</sup> calculated 394.1267, found 394.1266. <sup>1</sup>H NMR was consistent with previously reported values.<sup>[2]</sup> <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.9, 172.3, 172.0, 135.7, 133.3, 133.2, 128.3, 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.



**(2*S*,3*S*,4*S*,5*R*)-5-(4'-Bromo-phenyl)-pyrrolidine-**

**2,3,4-tricarboxylic acid trimethyl ester (4h)** Purified by column chromatography using SiO<sub>2</sub> and 10% Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> 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 min;  $\tau_{\text{minor}}$  = 39.7 min). Yield: 87%.  $[\alpha]_{\text{D}}^{\text{rt}}$  =

+12° (c = 0.26 g/100 mL, CH<sub>2</sub>Cl<sub>2</sub>, 68% ee). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 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<sub>2</sub>CH<sub>3</sub>), 3.76 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 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.



**(2*S*,3*S*,4*S*,5*R*)-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<sub>2</sub>Cl<sub>2</sub>. 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<sub>2</sub>. The excess *p*-toluenesulfonyl chloride was eluted with CH<sub>2</sub>Cl<sub>2</sub> after which the product was eluted with Et<sub>2</sub>O to give a quantative 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,  $\tau_{\text{major}} = 11.8$  min;  $\tau_{\text{minor}} = 16.1$  min).  $[\alpha]_{\text{D}}^{25} = +89.6^{\circ}$  ( $c = 0.115$  g/100 mL,  $\text{CH}_2\text{Cl}_2$ , 94.5% ee). HRMS  $\text{C}_{27}\text{H}_{27}\text{NO}_8\text{S}$   $[\text{M}+\text{Na}]^+$  calculated 548.1355, found 548.1360.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (s, 1H, ArH), 7.68 (m, 2H, ArH), 7.60 (d, 1H,  $J = 8.5$  Hz, ArH), 7.51 (d, 2H,  $J = 8.0$  Hz, ArH), 7.38 (m, 3H, ArH), 6.99 (d, 2H,  $J = 8.0$  Hz, ArH), 5.33 (d, 1H,  $J = 9.4$  Hz, H-5), 4.49 (d, 1H,  $J = 9.4$  Hz, H-2), 3.86 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 3.84 (dd, 1H,  $J = 9.4$  Hz,  $J = 10.9$  Hz, H-3), 3.66 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 3.59 (dd, 1H,  $J = 9.4$  Hz,  $J = 10.9$  Hz, H-4), 3.15 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 2.16 (s, 3H, ArCH<sub>3</sub>)  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  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  $\text{P2}_1$ , with unit cell at 120K:  $a = 9.7747(8)\text{\AA}$ ,  $b = 11.8018(9)\text{\AA}$ ,  $c = 10.4781(8)\text{\AA}$ ,  $\beta = 90.132(2)^{\circ}$ ,  $V = 1208.7(2)\text{\AA}^3$ ,  $Z = 2$ ,  $\rho_{\text{calcd}} = 1.444$ ,  $\mu = 1.88\text{cm}^{-1}$  (MoK $\alpha$  radiation,  $\lambda = 0.71073\text{\AA}$ ),  $F(000) = 552$ ,  $T = 120\text{K}$ .

16861 reflections collected on a SMART diffractometer, 6855 independent, 4712 significant ( $I > 3\sigma(I)$ ). Structure solved by means of the SIR97 program system.<sup>[6]</sup> Least squares refinement according to Rogers<sup>[7]</sup> 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](mailto:deposit@ccdc.cam.ac.uk)).

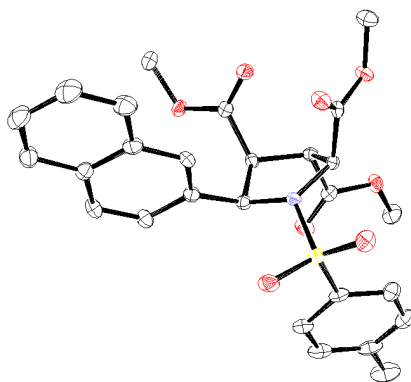


Table 1. Effect of solvent in the reaction of *N*-2-naphthylidene glycinate (**1b**) and methyl acrylate (**3a**) in the presence of Zn(OTf)<sub>2</sub> and ligand **5a**.

Entry <sup>a</sup>	Solvent	Ee (%)
1	Toluene	22.5
2	Et <sub>2</sub> O	24.5
3	CH <sub>2</sub> Cl <sub>2</sub>	65
4	THF	78
5	MeCN	61
6	<b>3a</b>	76

a: Zn(OTf)<sub>2</sub>, ligand **5a** and Et<sub>3</sub>N were used in 10 mol%.

Table 2. Effect of the amount of base in the Zn<sup>II</sup>-catalyzed reaction of *N*-2-naphthylidene glycinate (**1b**) and methyl acrylate (**3a**).

Entry <sup>a</sup>	Et <sub>3</sub> N (mol%)	Ee (%)
1	5	78.3
2	7.5	79.8
3	10	79.5
4	12.5	79.6
5	15	78.8
6	20	78.0

a: Zn(OTf)<sub>2</sub> and ligand **5a** was used in 10 mol%.

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