

Supplementary Information for  
**High-Throughput Determination of Enantiopurity in Atroposelective Synthesis of Aryl Triazoles**

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## General procedure

All reagents were purchased from commercial sources. Acetonitrile was spectrophotometric grade. All other solvents were ACS grade and used without further purification. Compounds **1**, **2**, and **3** were synthesized according to literature procedure.<sup>s1</sup> Compound characterization for these samples may be found in reference s1. Chiral HPLC data were acquired using an Agilent 1100 series analytical chiral HPLC equipped with a photodiode array detector (254 nm) with a Daicel Chiralpak IA column (5  $\mu$ m particle size, 4.5 x 250 mm), flow rate of 1.0 mL/min, and either 18% EtOH/hexanes (for compound **2**) or 20 % EtOH/hexanes (for compound **3**). CD screening of the atropisomers **1**, **2**, and **3** were performed using either a Jasco J-815 spectropolarimeter in the Targeted Therapeutic Drug Discovery and Development Program facility at the University of Texas at Austin or an Ekko CD microplate reader manufactured by Hinds Instruments. Titration study was conducted by using a Cary 100 UV-Vis spectrophotometer from Agilent Technology. HyperSep™ silica cartridges (bed weight 50 mg, column capacity 1 mL) were used for a wash-elute step. All stock solutions for CD analysis were prepared using acetonitrile as the solvent: **1** (17.5 mM), **2** (17.5 mM), **3** (16 mM), and Cu(OTf)<sub>2</sub> (17.5 mM for complexation with **1** and **2**, 16 mM for complexation with **3**).

## CD data collection parameters

**Jasco J-815 with auto peltier 6-cell changer:** Sample concentration in acetonitrile (1.75 mM for **1** and **2**, 1.6 mM for **3**), Type 21 macro cuvette with PTFE stopper (1 mm, UV quartz), sensitivity - standard, D.I.T. (integration time) - 1 sec, bandwidth - 1 nm, data pitch - 0.1 nm, scanning speed - 100 nm/min, accumulation - 2 times, temperature - measured at 20 °C

**Ekko:** Sample concentration in acetonitrile (1.75 mM for **2** and 1.6 mM for **3**), sample volume (40  $\mu$ L per well), quartz microplate with lid and sealing foil (96 wells, 6.6 mm diameter, well capacity 300  $\mu$ L, quartz glass, Hellma Analytics), 40 mdeg sensitivity, 2 s integration time, room temperature.

## Titration study

The titration study was carried out using a Cary 100 UV-Vis spectrophotometer from Agilent Technology (10 mm cell, UV quartz). The spectra were obtained at 320 nm where only the complexes can absorb light. The concentration of copper(II) triflate in acetonitrile was set to 0.175 mM. The absorbance curve reached a plateau at approximately 3:1 ligand–metal molar ratio.

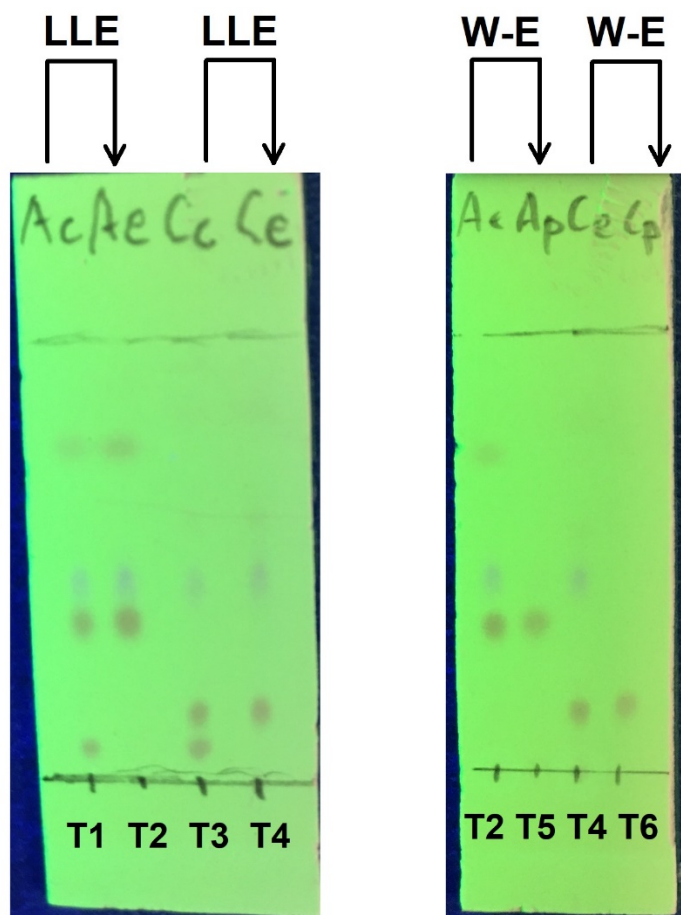
## Sample preparation protocol for HT *ee* determination

Four atroposelective syntheses were performed using (*R*)-/(*S*)-TCYP as the catalyst: Two reactions for **2** (*R*<sub>a</sub> and *S*<sub>a</sub>) and two reactions for **3** (*R*<sub>a</sub> and *S*<sub>a</sub>), respectively. The two reaction solutions were mixed in the different ratios such as 19:1, 18:2, 17:3, 15:5, 14:6, 12:8, 11:9, 9:11, 8:12, 6:14, 5:15, 3:17, 2:18, and 1:19, affording a total of 14 samples. Calibration curves were constructed with the varied *ee* values of **2** (-78, -46, -23, 1, 25, 49, and 80%) and **3** (-82, -50, -26, -2, 22, 46, and 78%), respectively. A sample preparation protocol for CD analysis is as follows:

- A crude solution (0.5 mg/mL) in DCM (2 mL) was washed 2 times with 2 mL of 0.01 M HCl (aq).
- A solution (1mL) in DCM layer was loaded onto the silica cartridge.
- Wash the cartridge with either 1:3 EA:Hex (3 x 1mL) for **2** or 1:4 EA:Hex (4 x 1mL) for **3**.
- Elute the product with 7:1 DCM:MeOH (200  $\mu$ L).
- Dry the sample with N<sub>2</sub>-blowing.
- Dissolve the dried sample in acetonitrile (2mL) and determine the concentration by measuring the UV absorbance (241 nm) of solution (200  $\mu$ L per well) with an Ekko microplate reader.

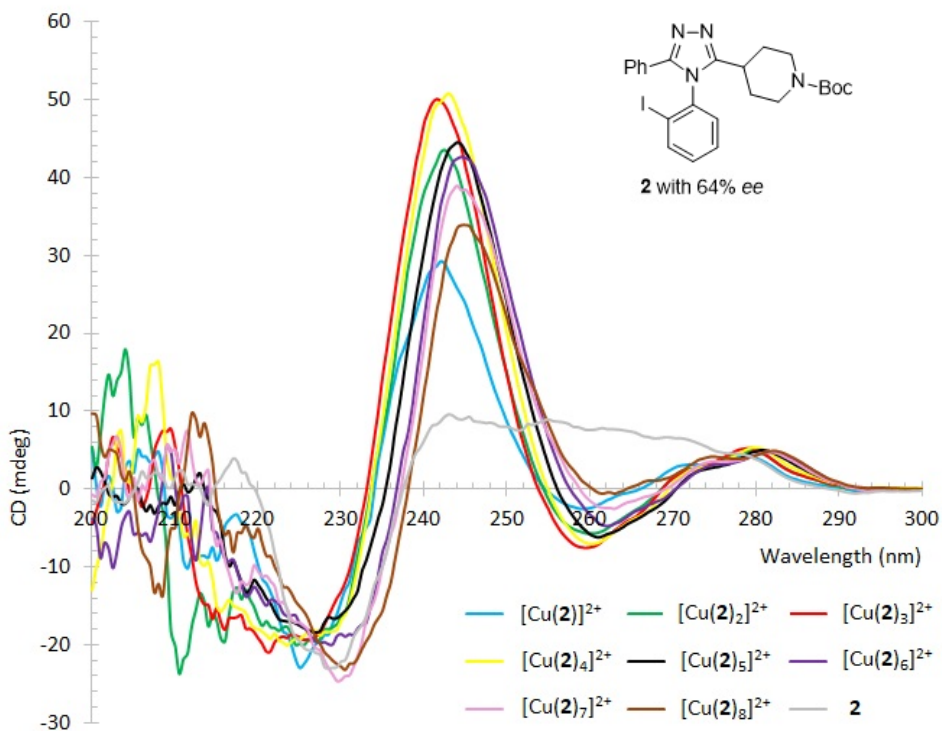
- A solution of copper(II) triflate in acetonitrile (3 eq.) was added to the solution.
- The concentration was adjusted to 1.75 mM for **2** and 1.6 mM for **3** by adding acetonitrile.
- A solution of the complex (40  $\mu$ L) was added to a 96-well plate and analyzed by a CD microplate reader.

### Thin layer chromatography analysis

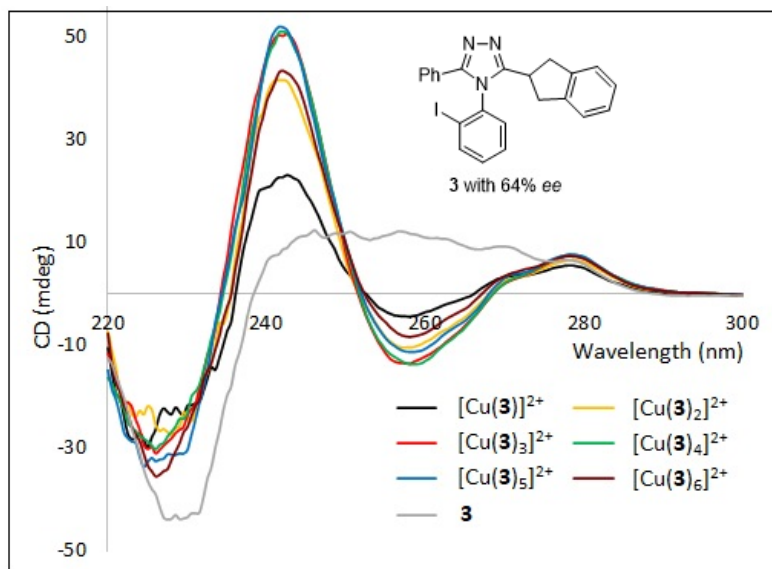


**Figure S1.** The sample purification process was monitored using thin layer chromatography (TLC). The TLC plates were developed in 1:1 EA:Hex: **T1** (the crude mixture of **3**), **T2** (the crude mixture **3** after liquid-liquid extraction (LLE)), **T3** (the crude mixture of **2**), **T4** (the crude mixture **2** after liquid-liquid extraction (LLE)), **T5** (the pure **3** after a wash-elute (W-E) step), **T6** (the pure **2** after a wash-elute (W-E) step).

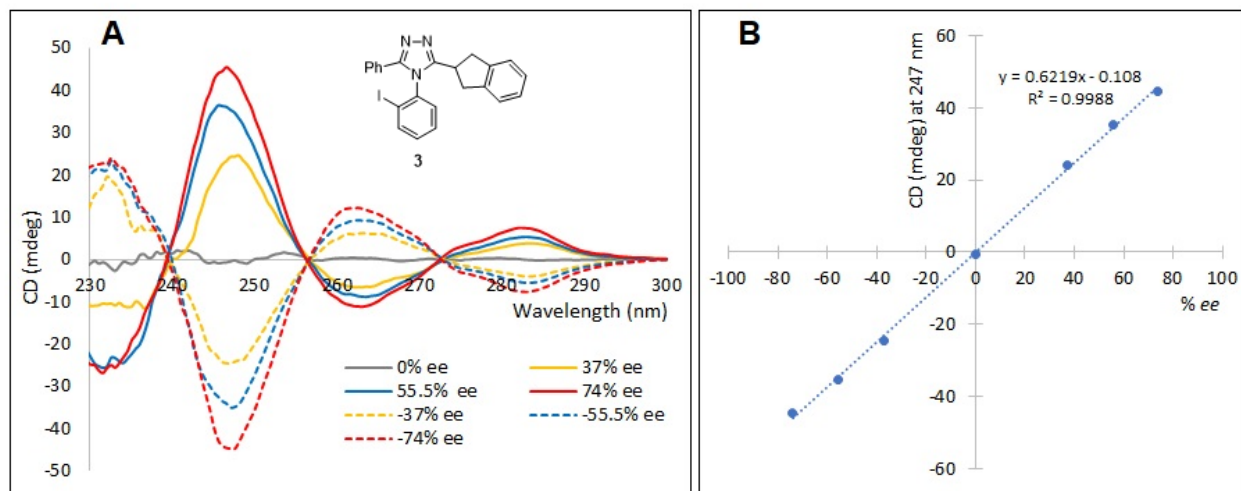
## Additional CD spectra



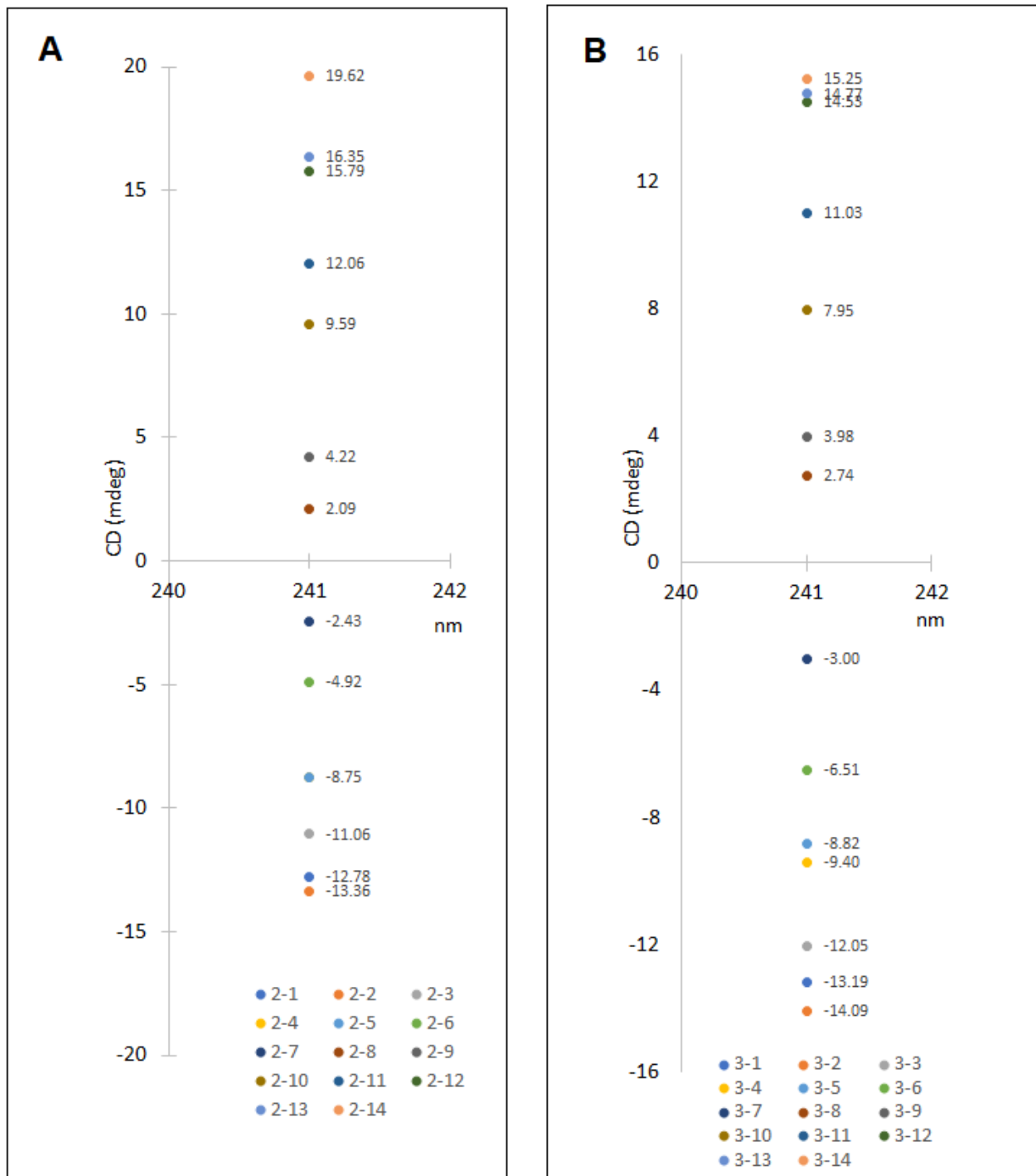
**Figure S2.** The CD spectra of **2** (64% ee) obtained with addition of copper(II) triflate (Jasco J-815, 1.75 mM in acetonitrile, 1 mm cell).



**Figure S3.** The CD spectra of **3** (64% ee) obtained with addition of copper(II) triflate (Jasco J-815, 1.6 mM in acetonitrile, 1 mm cell).



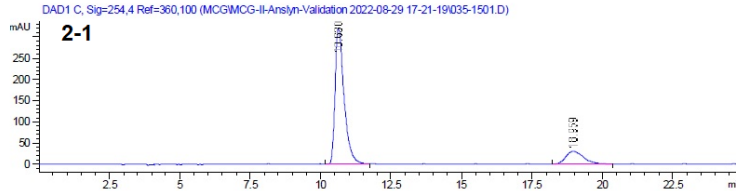
**Figure S4.** (A) CD spectra were recorded with  $[\text{Cu}(\mathbf{3})]\text{OTf}_2$  having known *ee* values (Jasco J-815, 1.6 mM in acetonitrile, 1 mm cell). (B) The calibration curve was linear, exhibiting  $R^2 = 0.9988$ .



**Figure S5.** (A) CD spectra in the HT *ee* determination of **2** (14 samples). (B) CD spectra in the HT *ee* determination of **3** (14 samples).

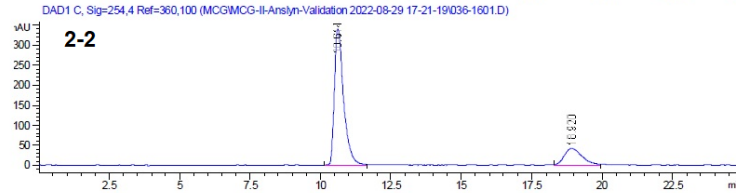
# Chiral HPLC spectra

## Chiral HPLC spectra for the 14 samples of 2 (2-1 ~ 2-14)



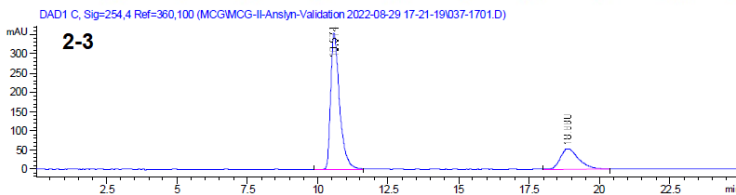
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.630        | VV   | 0.3364      | 7156.31348   | 320.60287    | 83.8279 |
| 2      | 18.959        | VV   | 0.6447      | 1380.59912   | 30.46684     | 16.1721 |



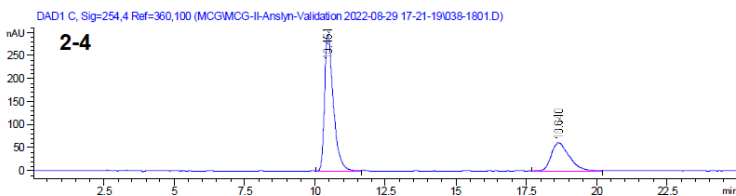
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.614        | VV   | 0.3433      | 7755.86182   | 341.07870    | 80.5476 |
| 2      | 18.920        | VV   | 0.6507      | 1873.05420   | 42.12535     | 19.4524 |



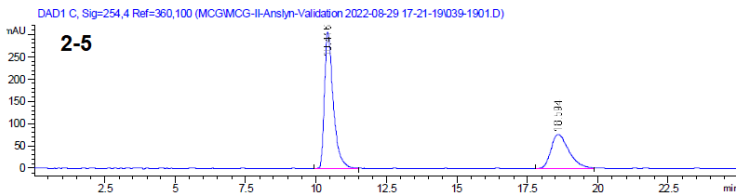
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.574        | VV   | 0.3306      | 7815.10889   | 355.30817    | 76.7090 |
| 2      | 18.880        | VB   | 0.6651      | 2372.89111   | 53.12338     | 23.2910 |



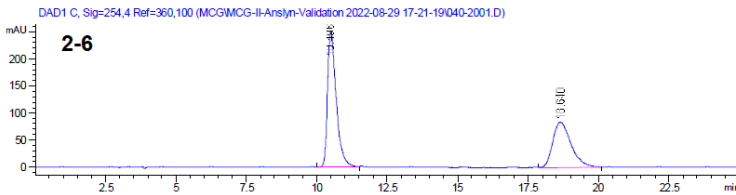
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.454        | VV   | 0.3296      | 6485.77295   | 296.06149    | 70.2052 |
| 2      | 18.640        | VB   | 0.6563      | 2752.52905   | 61.25091     | 29.7948 |



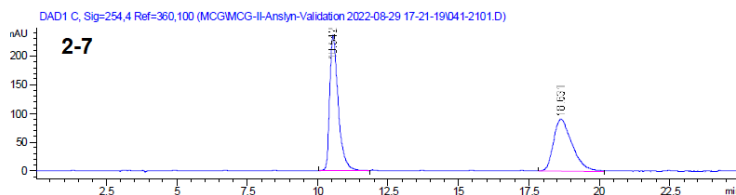
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.416        | VV   | 0.3288      | 6702.02832   | 306.84210    | 66.0801 |
| 2      | 18.594        | VV   | 0.6654      | 3440.25171   | 77.27299     | 33.9199 |



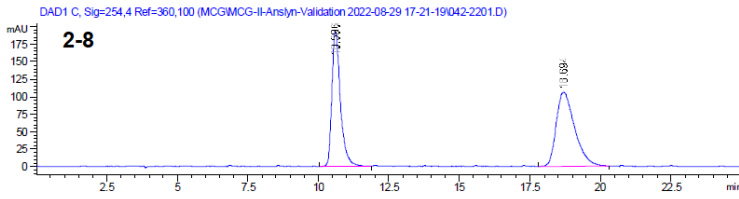
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.496        | VV   | 0.3285      | 5453.35986   | 252.01387    | 58.9103 |
| 2      | 18.640        | VV   | 0.6858      | 3803.69043   | 83.75817     | 41.0897 |



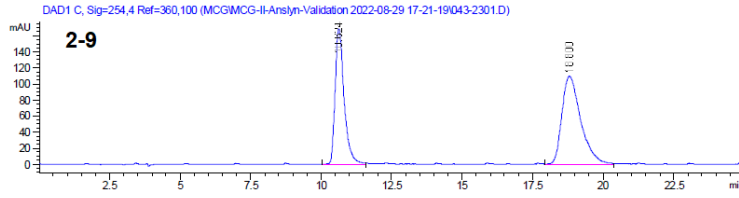
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.542        | VV   | 0.3187      | 5013.12939   | 237.05135    | 54.7529 |
| 2      | 18.631        | VV   | 0.6776      | 4142.78955   | 90.24062     | 45.2471 |



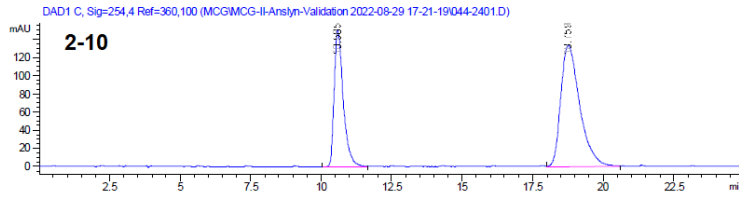
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.596        | VB   | 0.3126      | 4075.61206   | 194.39854    | 45.8098 |
| 2      | 18.694        | VB   | 0.6715      | 4821.19727   | 106.22992    | 54.1902 |



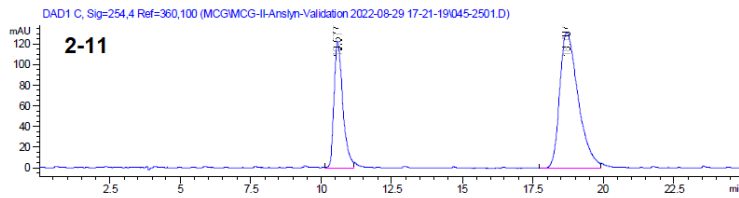
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.624        | VV   | 0.3359      | 3731.73120   | 168.81984    | 42.3044 |
| 2      | 18.800        | VV   | 0.7072      | 5089.40430   | 109.71995    | 57.6956 |



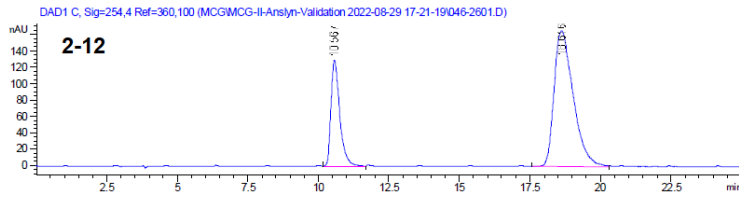
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.585        | VV   | 0.3374      | 3371.53174   | 150.50046    | 35.1043 |
| 2      | 18.759        | VV   | 0.7143      | 6232.79053   | 133.59401    | 64.8957 |



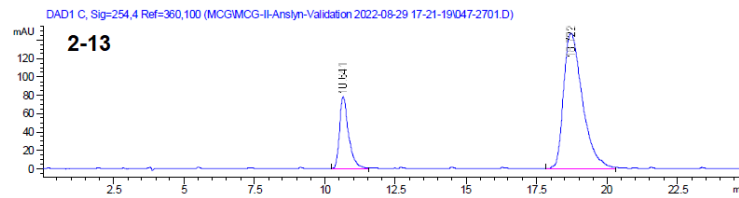
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.577        | VV   | 0.3281      | 2651.54883   | 122.70514    | 30.6872 |
| 2      | 18.707        | VV   | 0.6901      | 5989.02490   | 131.81387    | 69.3128 |



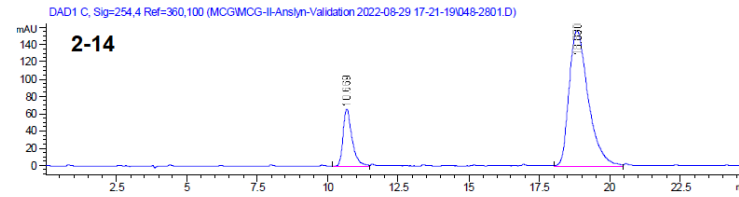
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.567        | VB   | 0.3271      | 2818.53369   | 129.93744    | 26.5113 |
| 2      | 18.616        | VV   | 0.7039      | 7812.89063   | 165.75615    | 73.4887 |



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.641        | VV   | 0.3386      | 1738.95117   | 77.85490     | 20.2768 |
| 2      | 18.722        | BV   | 0.7068      | 6837.09326   | 147.50235    | 79.7232 |

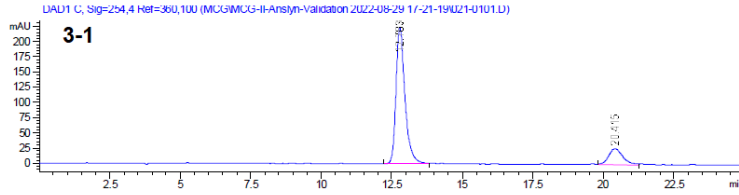


Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 10.669        | BV   | 0.3288      | 1454.25061   | 65.56335     | 16.4900 |
| 2      | 18.830        | VV   | 0.7211      | 7364.73340   | 156.48276    | 83.5100 |

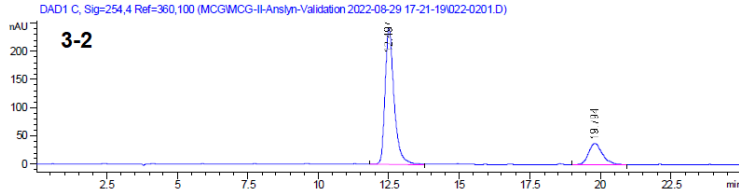


## Chiral HPLC spectra for the 14 samples of 3 (3-1 ~ 3-14)



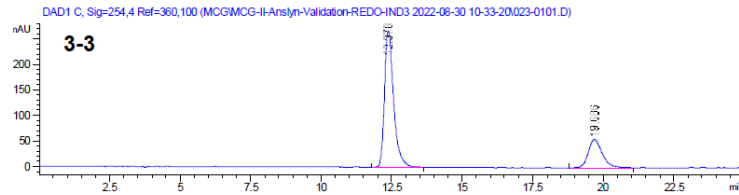
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.783        | VV   | 0.3326      | 4974.80762   | 224.47734    | 84.3558 |
| 2      | 20.415        | VV   | 0.5270      | 922.60400    | 26.44824     | 15.6442 |



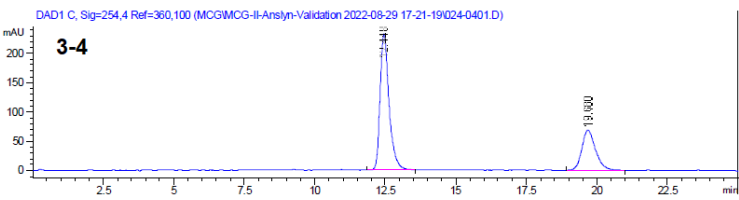
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.497        | VB   | 0.3327      | 5366.66064   | 241.99092    | 80.2191 |
| 2      | 19.794        | VV   | 0.5102      | 1323.34253   | 38.00810     | 19.7809 |



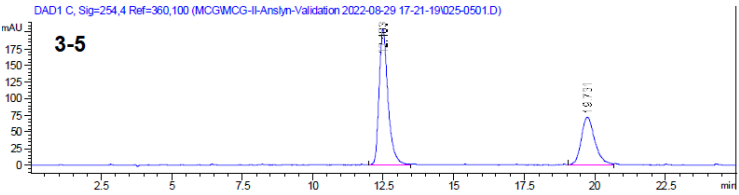
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.378        | VV   | 0.3370      | 6018.86816   | 269.01251    | 75.5999 |
| 2      | 19.686        | VV   | 0.5311      | 1942.60852   | 55.95198     | 24.4001 |



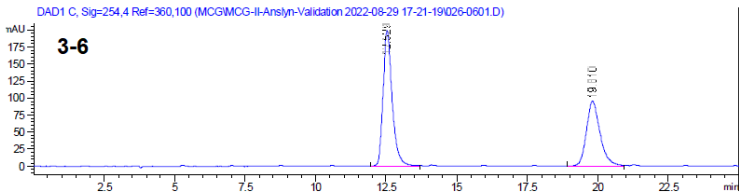
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.448        | BB   | 0.3302      | 5110.28271   | 232.70819    | 68.4748 |
| 2      | 19.680        | VB   | 0.5161      | 2352.73145   | 68.60339     | 31.5252 |



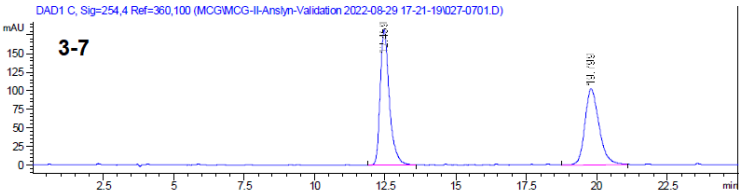
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.483        | VV   | 0.3360      | 4529.24658   | 204.79390    | 64.8512 |
| 2      | 19.731        | VV   | 0.5128      | 2454.81421   | 72.54388     | 35.1488 |



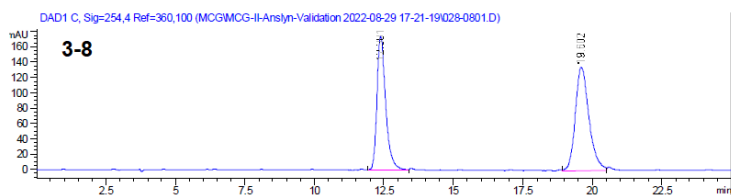
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.529        | VB   | 0.3348      | 4450.49268   | 199.09212    | 57.9989 |
| 2      | 19.810        | VV   | 0.5062      | 3222.92041   | 95.38564     | 42.0011 |



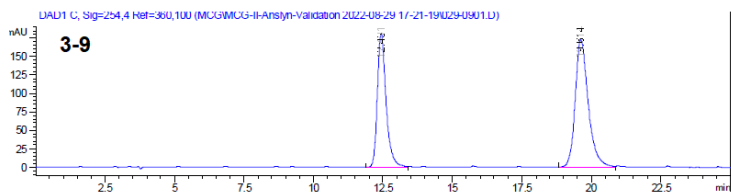
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.459        | VV   | 0.3398      | 4152.57324   | 183.62100    | 53.5099 |
| 2      | 19.799        | VV   | 0.5347      | 3607.80298   | 102.99853    | 46.4901 |



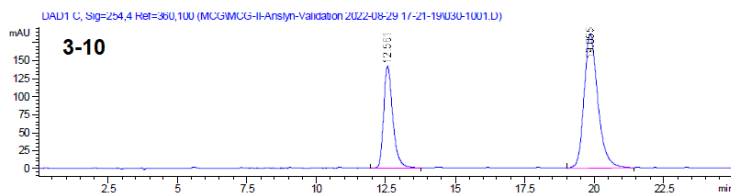
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.381        | VV   | 0.3297      | 3846.77954   | 175.50037    | 45.3656 |
| 2      | 19.602        | VV   | 0.5133      | 4632.72168   | 135.37120    | 54.6344 |



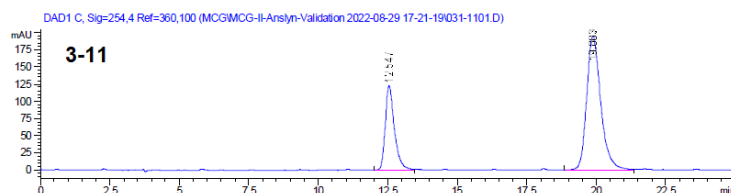
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.431        | VV   | 0.3254      | 3933.88086   | 181.08604    | 40.9219 |
| 2      | 19.614        | VV   | 0.5017      | 5679.25195   | 172.69193    | 59.0781 |



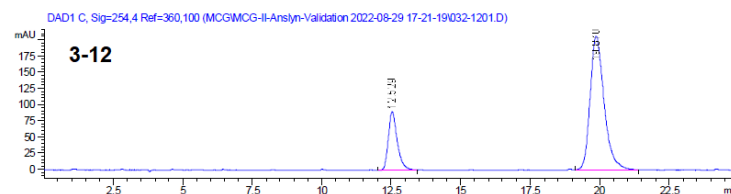
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.561        | VV   | 0.3514      | 3276.64014   | 141.91197    | 33.6548 |
| 2      | 19.855        | VV   | 0.5243      | 6459.38770   | 186.37651    | 66.3452 |



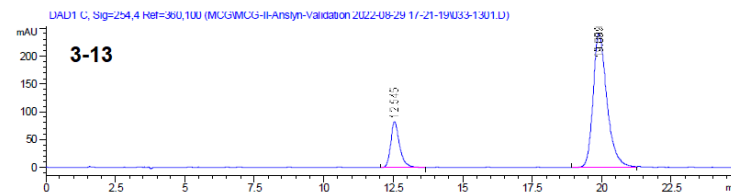
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.547        | BV   | 0.3456      | 2850.92065   | 123.35363    | 29.2665 |
| 2      | 19.883        | VV   | 0.5381      | 6890.33545   | 195.05988    | 70.7335 |



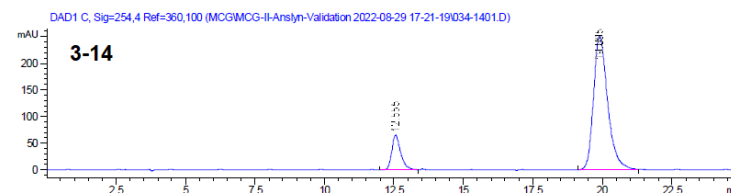
Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.529        | VV   | 0.3438      | 2063.26953   | 90.57732     | 21.9686 |
| 2      | 19.870        | VV   | 0.5347      | 7328.64893   | 207.15735    | 78.0314 |



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.545        | VB   | 0.3382      | 1858.58228   | 82.68276     | 18.1155 |
| 2      | 19.899        | VV   | 0.5242      | 8401.04199   | 241.30537    | 81.8845 |



Signal 3: DAD1 C, Sig=254,4 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area %  |
|--------|---------------|------|-------------|--------------|--------------|---------|
| 1      | 12.555        | VV   | 0.3442      | 1486.85327   | 65.16356     | 14.1697 |
| 2      | 19.895        | VV   | 0.5425      | 9006.30371   | 252.24724    | 85.8303 |

## References

- s1. Choi, S.; Guo, M. C.; Coombs, G. M.; Miller, S. J., Catalytic Asymmetric Synthesis of Atropisomeric N-Aryl 1,2,4-Triazoles. *J. Org. Chem.* 2023, DOI: 10.1021/acs.joc.1022c02727.