

## **Expanding Biohybrid-mediated Asymmetric Catalysis into the Realm of RNA**

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**Supporting Information**

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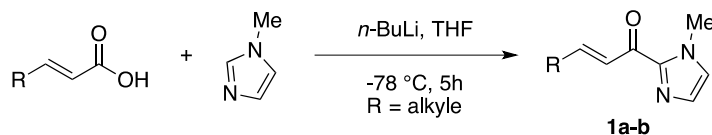
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## General Methods

The reactions were run under argon atmosphere in oven-dried glassware unless otherwise specified. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, Acros Organics or Alfa Aesar and used as received. L-5'-(UCAGGGCCCUGA)<sub>2</sub> (**ORN1**), D-5'-(UCAGGGCCCUGA)<sub>2</sub> (**ORN2**), L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**), D-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN4**), L-5'-(UCAGCAUGCAUGCAUGCAUGCUGA)<sub>2</sub> (**ORN5**) and L-5'-GUACGAAUUCGAAUCGUAACAGUCAGGCAGUCAGUCUUUUGACUGACUGCCUGACUGACUUCGAAUUCGUAC (**ORN6**), L-5'-(AAAAAAAAUUUUUUUU)<sub>2</sub> (**ORN7**), L-5'-(GGGGGGGGCCCCCCCC)<sub>2</sub> (**ORN8**), L-5'-(AAAAGGGGGCCCCUUUU)<sub>2</sub> (**ORN9**), L-5'-(GGGGUUUUAAAACCCC)<sub>2</sub> (**ORN10**), L-5'-(ACUAUCCGCGGAUAGU)<sub>2</sub> (**ORN11**) and L-5'-(GCCGAUUAUAAUCGGC)<sub>2</sub> (**ORN12**) were assembled on a RNA synthesizer and purified by ion exchange and reverse-phase HPLC. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et<sub>2</sub>O) were distilled from sodium/benzophenone. *N,N*-dimethylformamide (DMF) was distilled under vacuum over anhydrous MgSO<sub>4</sub>. Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck 60F254) visualized either with a UV lamp (254 nm) or by using solutions of *p*-anisaldehyde/sulfuric acid/acetic acid (AcOH) in ethanol (EtOH) or KMnO<sub>4</sub>/K<sub>2</sub>CO<sub>3</sub>/AcOH in water followed by heating. Flash chromatographies were performed on silica gel (60-230 mesh mesh). Organic extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> or MgSO<sub>4</sub>. Infrared spectra (IR) were recorded on a Bruker TENSOR™ 27 (IRTF) and wave-numbers are indicated in cm<sup>-1</sup>. <sup>1</sup>H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz in CDCl<sub>3</sub> (unless otherwise specified) and the observed signals are reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator (CDCl<sub>3</sub> δ 7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or overlap of nonequivalent resonances), integration. <sup>13</sup>C NMR spectra were recorded at 100 MHz in CDCl<sub>3</sub> (unless otherwise specified) and the observed signals were reported as follows: chemical shift in parts per million from tetramethylsilane with the solvent as an internal indicator (CDCl<sub>3</sub> δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH<sub>2</sub>, q = CH<sub>3</sub>). Coupling constants, *J*, are reported in hertz (Hz). All NMR spectra were obtained at room temperature unless otherwise specified. Enantiomeric excess determinations were performed by supercritical fluid chromatography (SFC) and HPLC analysis on chiral phase. The sign before the *ees* values is arbitrary. Mass spectra (MS) were recorded using a Hewlett-Packard tandem 5890A/5971 GCMS (70 eV). High-resolution mass spectra were performed by "Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris)".

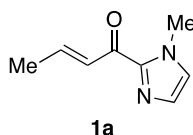
## Experimental and Spectral data

### General Procedure A. Synthesis of $\alpha,\beta$ -unsaturated acyl imidazoles **1a-b**



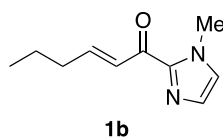
The  $\alpha,\beta$ -unsaturated substrates **1a** and **1b** were synthesized *via* a modification of the procedure originally reported by Evans and co-workers.<sup>1</sup> An oven-dried 250 mL round-bottomed flask under an argon atmosphere was charged with 1-methylimidazole (24 mmol, 2.4 equiv) and dry THF (50 mL). The solution was cooled to  $-78\text{ }^\circ\text{C}$  in a dry ice/acetone bath for 15 min, then *n*-BuLi (2.5 M in *n*-hexane, 24 mmol, 2.4 equiv) was added dropwise over 10 min. The mixture was warmed to rt and stirred for an additional 30 min, then cooled back to  $-78\text{ }^\circ\text{C}$ . The desired acid (10 mmol, 1 equiv) in dry THF (10 mL) was added dropwise over a 10 min period. The resulting solution was stirred at  $-78\text{ }^\circ\text{C}$  for 15 min, then warmed at rt and stirred for an additional 2 h. The reaction was quenched with a saturated aqueous solution of  $\text{NaHCO}_3$  solution (50 mL) and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 40 mL), dried over anhydrous  $\text{MgSO}_4$ , gravity filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography, eluting with EtOAc/pentane (4:6).

#### (*E*)-1-(1-Methyl-1*H*-imidazol-2-yl)but-2-en-1-one (**1a**)



**Following general procedure A.** 1-Methylimidazole (2g, 2.2 mL, 27.6 mmol), *n*-BuLi (2.5 M in *n*-hexane, 11 mL, 27.6 mmol) and crotonic acid (0.95 g, 11.4 mmol) in dry THF (60 mL). The title compound (molecular formula:  $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$ , MW = 150.18 g/mol, 0.91 g) as a colorless oil in 53% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>1</sup>

#### (*E*)-1-(1-Methyl-1*H*-imidazol-2-yl)hex-2-en-1-one (**1b**)

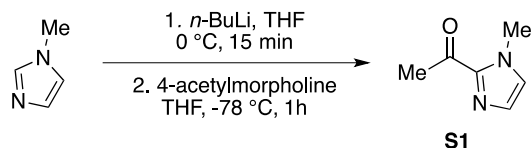


**Following general procedure A.** 1-Methylimidazole (1g, 1.1 mL, 12.8 mmol), *n*-BuLi

<sup>1</sup> D. A. Evans, K. R. Fandrick, H.-J. Song *J. Am. Chem. Soc.* **2005**, *127*, 8942-8943.

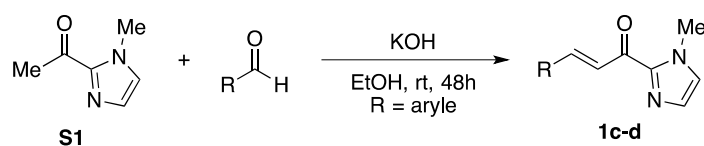
(2.5 M in *n*-hexane, 5.5 mL, 12.8 mmol) and (2*E*)-hexenoic acid (0.65 g, 0.7 mL, 5.7 mmol) in dry THF (60 mL). The title compound (molecular formula: C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O, MW = 178.23 g/mol, 0.505 g) as a colorless oil in 51% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>1</sup>

### Synthesis of 1-(1-methyl-1*H*-imidazol-2-yl)ethanone



Compound **S1** was synthesized *via* a modification of the procedure originally reported by Scheidt and co-workers.<sup>2</sup> An oven-dried 100 mL round-bottomed flask under an argon atmosphere was charged with 1-methylimidazole (4.5 g, 4.4 mL, 55.2 mmol, 1.1 equiv) and dry THF (60 mL). The solution was cooled to 0 °C in an ice bath for 15 min, then *n*-BuLi (2.5 M in *n*-hexane, 24 mL, 55.2 mmol, 1.1 equiv) was added dropwise over 10 min. The mixture was stirred at 0 °C for 15 min, then cannulated into a solution of 4-acetylmorpholine (6.5 g, 5.8 mL, 50.1 mmol, 1 equiv) in dry THF (40 mL) at -78 °C. The reaction mixture was then stirred at -78 °C for 1 h and quenched with a 1N aqueous solution of HCl (5 mL), stirred for 5 min and diluted with a saturated aqueous solution of NaHCO<sub>3</sub> (15 mL) and brine (15 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL) and the combined organic layers were dried over anhydrous MgSO<sub>4</sub>, gravity filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography, eluting with Et<sub>2</sub>O/pentane (9:1) to provide the title compound (molecular formula: C<sub>6</sub>H<sub>8</sub>N<sub>2</sub>O, MW = 124.14 g/mol, 6.2 g) as a colorless oil in 79% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>2</sup>

### General procedure B. Synthesis of $\alpha,\beta$ -unsaturated substrates **1c-d**

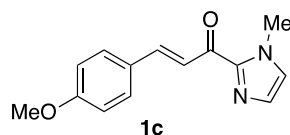


The  $\alpha,\beta$ -unsaturated substrates **1c-d** were synthesized *via* a modification of the procedure originally reported by Scheidt and co-workers.<sup>2</sup> An oven-dried 100 mL round-bottomed flask under an argon atmosphere was charged with 1-methylimidazole (10.0 mmol, 1.0 equiv) and EtOH (20 mL). The appropriate aromatic aldehyde (10.0 mmol, 1.0 equiv) and a catalytic amount of KOH (2 mmol, 0.2 equiv) were added and the solution was stirred at rt for 48 h. The formation of a precipitate was observed. The reaction was quenched with H<sub>2</sub>O (50 mL) and the aqueous phase was

<sup>2</sup> M. C. Myers, A. R. Bharadwaj, B. C. Milgram, K. A. Scheidt *J. Am. Chem. Soc.* **2005**, *127*, 14675-14680.

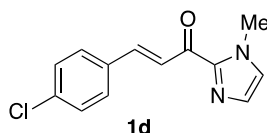
extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (2 x 50 mL), dried over anhydrous MgSO<sub>4</sub>, gravity filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography over silica gel using EtOAc/pentane (1:1) as the eluent.

**(E)-3-(4-Methoxyphenyl)-1-(1-methyl-1H-imidazol-2-yl)prop-2-en-1-one (1c)**



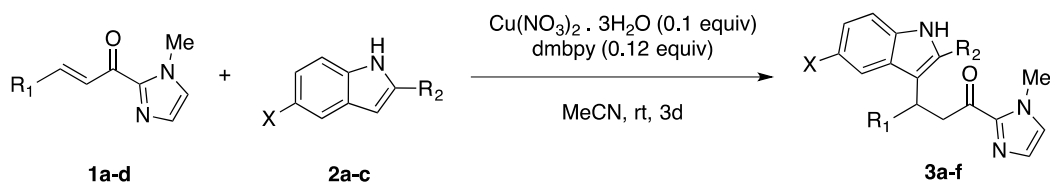
Following the general procedure B. S1 (1.3 g, 10.5 mmol), 4-methoxybenzaldehyde (1.4 g, 1.3 mL, 10.5 mmol) and KOH (0.11 g, 2 mmol), in EtOH (20 mL). The title compound (molecular formula: C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>, MW = 242.27 g/mol, 1.3 g) was isolated as a yellow solid in 51% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>2</sup>

**(E)-3-(4-Chlorophenyl)-1-(1-methyl-1H-imidazol-2-yl)prop-2-en-1-one (1d)**



Following the general procedure B. S1 (1.3 g, 10.5 mmol), 4-chlorobenzaldehyde (1.47 g, 10.5 mmol) and KOH (0.11 g, 2 mmol), in EtOH (20 mL). The title compound (molecular formula: C<sub>13</sub>H<sub>11</sub>ClN<sub>2</sub>O, MW = 246.69 g/mol, 1.7 g) was isolated as a white solid in 67% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>2</sup>

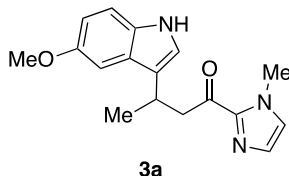
**General Procedure C. Racemic Friedel-Crafts alkylations**



An oven-dried 25 mL round-bottomed flask was charged with Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (0.035 mmol, 0.1 equiv), 4,4'-dimethyl-2,2'-bipyridyl (dmbpy, 0.042 mmol, 0.12 equiv) and MeCN (5 mL). The mixture was stirred at rt for 10 min then the α,β-unsaturated substrate (0.35 mmol, 1.0 equiv) and the desired indole (0.53 mmol, 1.5 equiv) were added. The solution was stirred at rt for 3 d. The reaction was eventually diluted with brine (10 mL) and extracted with Et<sub>2</sub>O (3 x 5 mL). The combined organic layers dried over anhydrous MgSO<sub>4</sub>, gravity filtered and concentrated under reduced pressure. The

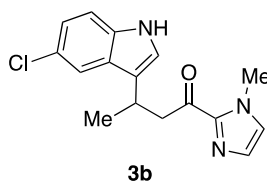
crude product was purified by flash chromatography over silica gel using EtOAc/pentane (1:1) as the eluent.

### 3-(5-Methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (3a)



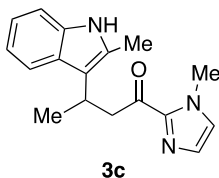
Following the general procedure C. **1a** (0.053 g, 0.35 mmol), 5-methoxyindole **2a** (0.078 g, 0.53 mmol), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (0.008 g, 0.035 mmol), 4,4'-dimethyl-2,2'-bipyridyl (0.008 g, 0.042 mmol) and MeCN (5 mL). The title compound (molecular formula: C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>, MW = 297.35 g/mol, 0.094 g) was isolated as a brown solid in 91% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>3</sup>

### 3-(5-Chloro-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (3b)



Following the general procedure C. Compound **1a** (0.020 g, 0.133 mmol), 5-chloroindole **2b** (0.024 g, 0.160 mmol), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (0.0032 g, 0.013 mmol), 4,4'-dimethyl-2,2'-bipyridyl (0.0034 g, 0.019 mmol), and MeCN (0.5 mL). The title compound (molecular formula: C<sub>16</sub>H<sub>16</sub>ClN<sub>3</sub>O, MW = 301.77 g/mol, 0.040 g) was isolated as a brown oil in quantitative yield. Spectroscopic data were consistent with the literature data for this compound.<sup>3</sup>

### 1-(1-Methyl-1*H*-imidazol-2-yl)-3-(2-methyl-1*H*-indol-3-yl)butan-1-one (3c)

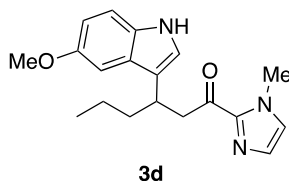


Following the general procedure C. **1a** (0.028 g, 0.186 mmol), 2-methylindole **2c** (0.037 g, 0.280 mmol), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (0.0045 g, 0.017 mmol), 4,4'-dimethyl-2,2'-bipyridyl

<sup>3</sup> Benedetti, E.; Duchemin, N.; Bethge, L.; Vonhoff, S.; Klussmann, S.; Vasseur, J.-J.; Cossy, J.; Smietana, M.; Arseniyadis, S. *Chem. Commun.* **2015**, *51*, 6076-6079.

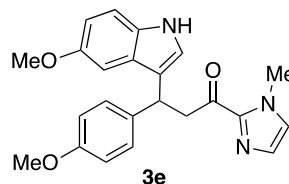
(0.0048 g, 0.026 mmol), and MeCN (0.7 mL). The title compound (molecular formula: C<sub>17</sub>H<sub>19</sub>N<sub>3</sub>O, MW: 281.35 g/mol, 0.034 g) was isolated as a brown oil in 65% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>4</sup>

### 3-(5-Methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)hexan-1-one (3d)



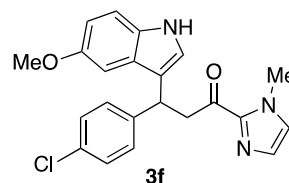
**Following the general procedure C.** **1b** (0.020 g, 0.112 mmol), 5-methoxyindole **2a** (0.025 g, 0.168 mmol), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (0.0027 g, 0.011 mmol), 4,4'-dmbpy (0.0029 g, 0.016 mmol), and MeCN (0.5 mL). The title compound (molecular formula: C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub>, MW: 325.40 g/mol, 0.025 g) was isolated as a brown oil in 68% yield. Spectroscopic data were consistent with the literature data for this compound.<sup>3</sup>

### 3-(5-Methoxy-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-(1-methyl-1*H*-imidazol-2-yl)propan-1-one (3e)



**Following the general procedure C.** **1c** (0.085 g, 0.35 mmol), 5-methoxyindole **2a** (0.078 g, 0.53 mmol), Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (0.008 g, 0.035 mmol), 4,4'-dimethyl-2,2'-bipyridyl (0.008 g, 0.042 mmol) and MeCN (5 mL). The title compound (molecular formula: C<sub>23</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>, MW = 389.45 g/mol, 0.135 g) was isolated as a brown solid in quantitative yield. Spectroscopic data were consistent with the literature data for this compound.<sup>3</sup>

### 3-(4-Chlorophenyl)-3-(5-methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)propan-1-one (3f)



<sup>4</sup> Boersma, A. J.; Feringa, B. L.; Roelfes, G. *Angew. Chem, Int. Ed.* **2009**, *48*, 3346-3348.



**Following the general procedure C.** **1d** (0.086 g, 0.35 mmol), 5-methoxyindole **2a** (0.078 g, 0.53 mmol),  $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  (0.008 g, 0.035 mmol), 4,4'-dimethyl-2,2'-bipyridyl (0.008 g, 0.042 mmol) and MeCN (5 mL). The title compound (molecular formula:  $\text{C}_{22}\text{H}_{20}\text{ClN}_3\text{O}_2$ , MW = 393.87 g/mol, 0.137 g) was isolated as a brown solid in quantitative yield. Spectroscopic data were consistent with the literature data for this compound.<sup>3</sup>

#### **Preparation of a 20 mM MOPS buffer (pH 6.5)**

209 mg of 3-(*N*-morpholino)propanesulfonic acid (MOPS, MW = 209.26 g/mol) were dissolved in 10 mL of  $\text{H}_2\text{O}$  MilliQ to obtain a 0.1 M solution. 1.9 mL of a 0.1 M solution of KOH (MW = 56.11 g/mol) in  $\text{H}_2\text{O}$  MilliQ was added followed by 38.1 mL of  $\text{H}_2\text{O}$  MilliQ.

#### **Preparation of a 20 mM MOPS buffer (pH 7.5)**

209 mg of 3-(*N*-morpholino)propanesulfonic acid (MOPS, MW = 209.26 g/mol) were dissolved in 20 mL of  $\text{H}_2\text{O}$  MilliQ and the pH was adjusted to 7.5 using a 0.1 M solution of KOH (MW = 56.11 g/mol). To the resulting solution was added a given volume of  $\text{H}_2\text{O}$  MilliQ to obtain the desired concentration.

#### **Preparation of a 10 mM $\text{MgCl}_2$ solution in 20 mM MOPS buffer (pH 6.5)**

4.8 mg of magnesium chloride anhydrous (MW = 95.21 g/mol) were dissolved in 5 mL of the previously prepared 20 mM MOPS buffer (pH 6.5).

#### **Preparation of a 50 mM MOPS buffer (pH 6.5)**

470 mg of 3-(*N*-morpholino)propanesulfonic acid (MOPS, MW = 209.26 g/mol) were dissolved in 20 mL of  $\text{H}_2\text{O}$  MilliQ and the pH was adjusted to 6.5 using a 0.1 M solution of KOH (MW = 56.11 g/mol). To the resulting solution was added a given volume of  $\text{H}_2\text{O}$  MilliQ to obtain the desired concentration.

#### **Preparation of a a 50 mM MOPS buffer (pH 7.5)**

470 mg of 3-(*N*-morpholino)propanesulfonic acid (MOPS, MW = 209.26 g/mol) were dissolved in 20 mL of  $\text{H}_2\text{O}$  MilliQ and the pH was adjusted to 7.5 using a 0.1 M solution of KOH (MW = 56.11 g/mol). To the resulting solution was added a given volume of  $\text{H}_2\text{O}$  MilliQ to obtain the desired concentration.

### Preparation of a 100 mM Tris buffer (pH 7.5)

300 mg of tris(hydroxymethyl)aminomethane acid (Tris, MW = 121.14 g/mol) were dissolved in 20 mL of H<sub>2</sub>O MilliQ and the pH was adjusted to 7.5 using a 1N aqueous solution of HCl (MW = 36.46 g/mol). To the resulting solution was added a given volume of H<sub>2</sub>O MilliQ to obtain the desired concentration.

### Preparation of [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] stock solution

4.5 mg of Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (MW = 241.60 g/mol) and 4 mg of 4,4'-dimethyl-2,2'-bipyridyl (dmbpy, MW = 184.24 g/mol) were dissolved in 3.3 mL of the previously prepared 20 mM MOPS buffer (pH 6.5). The mixture was stirred at rt for 5 h in a sealed tube under air. 1.8 mL of this solution were then transferred to another vial and diluted with 8.2 mL of the 20 mM MOPS buffer (pH 6.5).

### Preparation of a [Cu(ligand)] stock solution

2.2 mg of Cu(NO<sub>3</sub>)<sub>2</sub>·3H<sub>2</sub>O (MW = 241.60 g/mol) and the appropriate ligand (0.010 mmol) were dissolved in 8.3 mL of the previously prepared 20 mM MOPS buffer (pH 6.5). The resulting solution was sonicated for 30 min and stirred by inversion for 12 h.

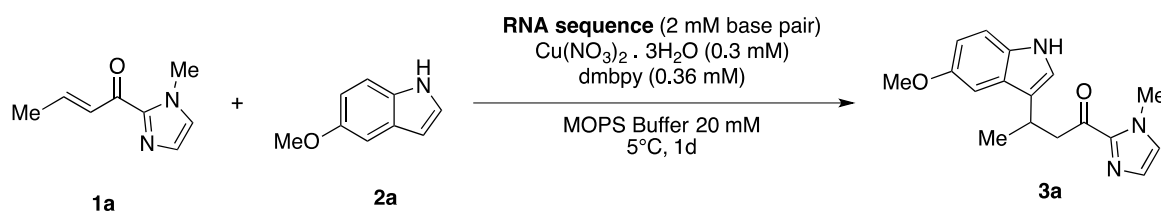
### Preparation of a 28.6 mM MOPS buffer (pH 6.5)

209 mg of 3-(*N*-morpholino)propanesulfonic acid (MOPS, MW = 209.26 g/mol) were dissolved in 10 mL of H<sub>2</sub>O MilliQ to obtain a 0.1 M solution. 1.9 mL of a 0.1 M solution of KOH (MW = 56.11 g/mol) in H<sub>2</sub>O MilliQ was added followed by 23 mL of H<sub>2</sub>O MilliQ.

### Preparation of the co-solvent stock solution

2.3 mL of the previously prepared 28.6 mM MOPS buffer (pH 6.5) were added to 1 mL of the appropriate co-solvent.

### General Procedure D. Enantioselective Friedel-Crafts alkylations using different RNA sequences



To a 3 mM base pair solution of the desired RNA sequence in a 20 mM MOPS buffer (400  $\mu$ L) was added a 0.9 mM solution of [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] in a 20 mM MOPS buffer (200  $\mu$ L). The resulting solution (2 mM base pair, 600  $\mu$ L) was cooled to 5 °C. To the cold mixture was added a 0.5 M solution of enone in MeCN (1.2  $\mu$ L), followed by a 2.5 M solution of substituted indole in MeCN (1.2  $\mu$ L). The reaction was mixed by inversion at 5 °C in a cold room. After 1 d, the mixture was warmed to rt and extracted with Et<sub>2</sub>O (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through a plug of silica gel and concentrated under reduced pressure, to give the crude product which was subjected to SFC analysis without further purification.

Entry	Sequence	Conversion <sup>a</sup> (%)	ee <sup>a</sup> (%)
1	ORN1	>99	0
2	ORN2	>99	0
3	ORN3	>99	(-) 40
4	ORN4	>99	(+) 40
5	ORN5	>99	0
6	ORN6	4	-

<sup>a</sup> Determined by chiral SFC analysis.

- **Following the general procedure D.** L-5'-(UCAGGGCCCUGA)<sub>2</sub> (**ORN1**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and racemic product [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 9.26 min; minor enantiomer  $t_R$  = 6.10 min].
- **Following the general procedure D.** D-5'-(UCAGGGCCCUGA)<sub>2</sub> (**ORN2**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and racemic product [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 9.26 min; minor enantiomer  $t_R$  = 6.10 min].
- **Following the general procedure D.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and

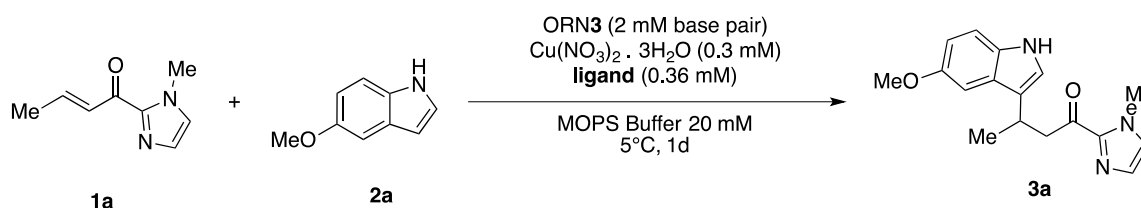
MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (–) 40% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 5.80 min; minor enantiomer  $t_R$  = 8.85 min].

- **Following the general procedure D.** D-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN4**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (+) 40% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 7.49 min; minor enantiomer  $t_R$  = 5.15 min].
- **Following the general procedure D.** L-5'-(UCAGCAUGCAUGCAUGCAUGCUGA)<sub>2</sub> (**ORN5**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and racemic product [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 7.49 min; minor enantiomer  $t_R$  = 5.15 min].
- **Following the general procedure D.** L-5'-GUACGAAUUCGAAGUCAGUCAGGCAGUCA GUCUUUUGACUGACUGCCUGACUGACUUCGAAUUCGUAC (**ORN6**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and racemic product [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 7.49 min; minor enantiomer  $t_R$  = 5.15 min].
- **Following the general procedure D:** L-5'-(AAAAAAAAUUUUUUU)<sub>2</sub> (**ORN7**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 6:94 and an enantiomeric excess of (–) 9% [Reprosil Chiral NR column; flow: 1.0 mL/min; *n*-Heptane/*i*-PrOH gradient;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 18.01 min; minor enantiomer  $t_R$  = 21.60 min].
- **Following the general procedure D:** L-5'-(GGGGGGGGCCCCCCC)<sub>2</sub> (**ORN8**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio

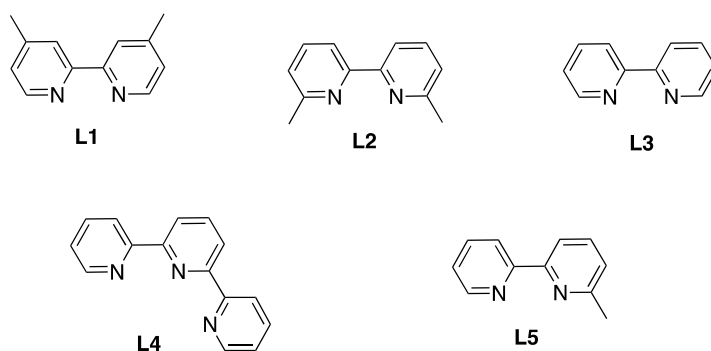
between **1a** and **3a** of 2:98 and an enantiomeric excess of (-) 18% [Reprosil Chiral NR column; flow: 1.0 mL/min; *n*-Heptane/*i*-PrOH gradient;  $\lambda = 220$  nm; major enantiomer  $t_R = 19.207$  min; minor enantiomer  $t_R = 22.469$  min].

- **Following the general procedure D:** L-5'-(AAAAGGGGCCCUUUU)<sub>2</sub> (**ORN9**) (**ORN9**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 4:96 and an enantiomeric excess of (-) 14% [Reprosil Chiral NR column; flow: 1.0 mL/min; *n*-Heptane/*i*-PrOH gradient;  $\lambda = 220$  nm; major enantiomer  $t_R = 18.64$  min; minor enantiomer  $t_R = 22.23$  min].
- **Following the general procedure D:** L-5'-(GGGGUUUAAAACCCC)<sub>2</sub> (**ORN10**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 4:96 and an enantiomeric excess of (-) 28% [Reprosil Chiral NR column; flow: 1.0 mL/min; *n*-Heptane/*i*-PrOH gradient;  $\lambda = 220$  nm; major enantiomer  $t_R = 18.61$  min; minor enantiomer  $t_R = 22.24$  min].
- **Following the general procedure D:** L-5'-(ACUAUCCGCGGAUAGU)<sub>2</sub> (**ORN11**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 4:96 and an enantiomeric excess of (-) 14% [Reprosil Chiral NR column; flow: 1.0 mL/min; *n*-Heptane/*i*-PrOH gradient;  $\lambda = 220$  nm; major enantiomer  $t_R = 18.64$  min; minor enantiomer  $t_R = 22.23$  min].
- **Following the general procedure D:** L-5'-(GCCGAUUAAUUCGGC)<sub>2</sub> (**ORN12**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 4:96 and an enantiomeric excess of (-) 19% [Reprosil Chiral NR column; flow: 1.0 mL/min; *n*-Heptane/*i*-PrOH gradient;  $\lambda = 220$  nm; major enantiomer  $t_R = 18.64$  min; minor enantiomer  $t_R = 22.26$  min].

## General Procedure E. Enantioselective Friedel-Crafts alkylations using different ligands



To a 3 mM base pair solution of L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**), in a 20 mM MOPS buffer (400  $\mu$ L) was added the desired 0.9 mM solution of [Cu(ligand)(NO<sub>3</sub>)<sub>2</sub>] in a 20 mM MOPS buffer (200  $\mu$ L). The resulting solution (2 mM base pair, 600  $\mu$ L) was cooled to 5 °C. To the cold mixture was added a 0.5 M solution of enone in MeCN (1.2  $\mu$ L), followed by a 2.5 M solution of substituted indole in MeCN (1.2  $\mu$ L). The reaction was mixed by inversion at 5 °C in a cold room. After 1 d, the mixture was warmed to rt and extracted with Et<sub>2</sub>O (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through a plug of silica gel and concentrated under reduced pressure, to give the crude product which was subjected to SFC analysis without further purification.



Entry	Ligand	Conversion <sup>a</sup> (%)	ee <sup>a</sup> (%)
1	L1	>99	(-) 40
2	L2	69	(-) 2
3	L3	>99	(-) 18
4	L4	>99	0
5	L5	>99	(-) 5

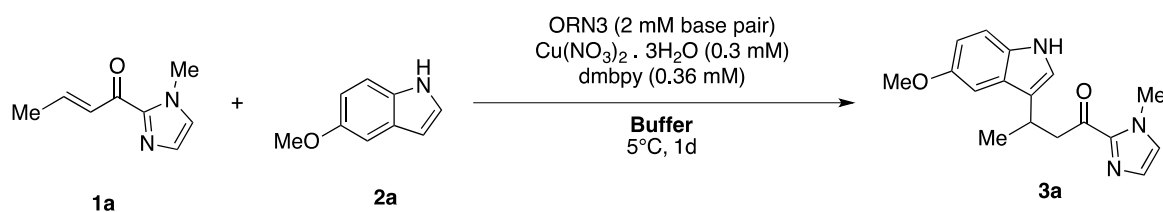
<sup>a</sup>Determined by chiral SFC analysis.

- **Following the general procedure E.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(L1)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and

**3a** of 0:100 and an enantiomeric excess of (-) 40 % [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 5.80$  min; minor enantiomer  $t_R = 8.85$  min].

- **Following the general procedure E.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(L2)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 31:69 and an enantiomeric excess of (-) 2 % [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 5.68$  min; minor enantiomer  $t_R = 8.50$  min].
- **Following the general procedure E.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(L3)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (-) 18 % [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 5.71$  min; minor enantiomer  $t_R = 8.74$  min].
- **Following the general procedure E.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(L4)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. HPLC analysis of the crude residue indicated a ratio between **1a** and **3a** of 1:100 and racemic product [DAICEL AD-H column; flow: 1.0 mL/min; Hex/*i*-PrOH;  $\lambda = 220$  nm; first enantiomer  $t_R = 16.18$  min; second enantiomer  $t_R = 21.17$  min].
- **Following the general procedure E.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole (5 mM), [Cu(L5)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. HPLC analysis of the crude residue indicated a ratio between **1a** and **3a** of 1:100 and an enantiomeric excess of (-) 5% [DAICEL AD-H column; flow: 1.0 mL/min; Hex/*i*-PrOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 20.92$  min; minorenantiomer  $t_R = 16.12$  min].

## General Procedure F. Enantioselective Friedel-Crafts alkylations using different buffers



To a 3 mM base pair solution of L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) in the desired buffer (400  $\mu$ L) was added the desired 0.9 mM solution of [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] in the desired buffer (200  $\mu$ L). The resulting solution (2 mM base pair, 600  $\mu$ L) was cooled to 5 °C. To the cold mixture was added a 0.5 M solution of enone in MeCN (1.2  $\mu$ L), followed by a 2.5 M solution of substituted indole in MeCN (1.2  $\mu$ L). The reaction was mixed by inversion at 5 °C in a cold room. After 1 d, the mixture was warmed to rt and extracted with Et<sub>2</sub>O (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered through a plug of silica gel and concentrated under reduced pressure, to give the crude product which was subjected to SFC analysis without further purification.

Entry	Buffer	Conversion <sup>a</sup> (%)	ee <sup>a</sup> (%)
1	MOPS (20 mM pH 6.5)	>99	(-) 40
2	MOPS (20 mM pH 7.5)	>99	(-) 25
3	MOPS (50 mM pH 6.5)	>99	(-) 40
4	MOPS (50 mM pH 7.5)	>99	(-) 6
5	Tris (100 mM pH 7.5)	>99	(-) 8
6	MOPS (20 mM pH 6.5) , MgCl <sub>2</sub> (10 mM)	>99	(+) 13

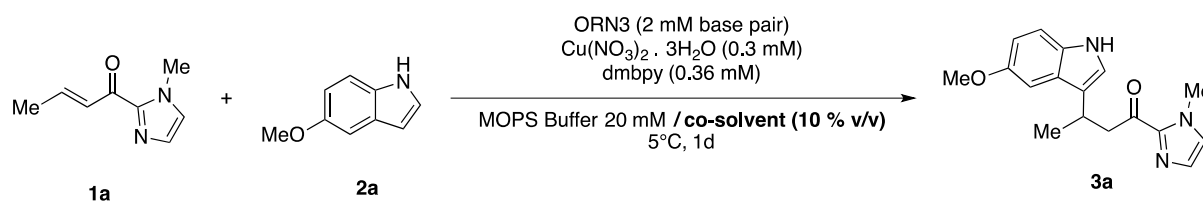
<sup>a</sup>Determined by chiral SFC analysis.

- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 6.5, 600  $\mu$ L); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (-) 40% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 5.80 min; minor enantiomer  $t_R$  = 8.85 min].



- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (20 mM, pH 7.5, 600 μL); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (-) 25% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 6.21 min; minor enantiomer t<sub>R</sub> = 9.28 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (50 mM, pH 6.5, 600 μL); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (-) 40% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 6.18 min; minor enantiomer t<sub>R</sub> = 9.22 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MOPS buffer (50 mM, pH 7.5, 600 μL); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (-) 6% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 6.21 min; minor enantiomer t<sub>R</sub> = 9.28 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and Tris Buffer (100 mM, pH 7.5, 600 μL); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (-) 8% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 6.04 min; minor enantiomer t<sub>R</sub> = 8.72 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbipy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM) and MgCl<sub>2</sub> (10 mM) MOPS (20 mM, pH 6.5, 600 μL); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (+) 13% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 8.69 min; minor enantiomer t<sub>R</sub> = 6.02 min].

## General Procedure G. Enantioselective Friedel-Crafts alkylations with co-solvents



To a 6 mM base pair solution of L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) in MOPS buffer (20 mM, pH 6.5) (200  $\mu\text{L}$ ) was added the co-solvent stock solution (200  $\mu\text{L}$ ) and the 0.9 mM solution of  $[\text{Cu}(\text{dmbpy})(\text{NO}_3)_2]$  in MOPS buffer (20 mM, pH 6.5) (200  $\mu\text{L}$ ). The resulting solution (2 mM base pair, 600  $\mu\text{L}$ ) was cooled to 5 °C. To the cold mixture was added a 0.5 M solution of enone in MeCN (1.2  $\mu\text{L}$ ), followed by a 2.5 M solution of substituted indole in MeCN (1.2  $\mu\text{L}$ ). The reaction was mixed by inversion at 5 °C in a cold room. After 1 d, the mixture was warmed to rt and extracted with  $\text{Et}_2\text{O}$  (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over  $\text{Na}_2\text{SO}_4$  to give the crude product which was subjected to SFC analysis without further purification.

Entry	Co-solvent (% v/v)	Conversion <sup>a</sup> (%)	ee <sup>a</sup> (%)
1	DMSO (10)	91	(-) 30
2	DMF (10)	>99	(-) 30
3	1,4 - Dioxane (10)	>99	(-) 30
4	Acetone (10)	>99	(-) 42
5	EtOH (10)	>99	(-) 32
6	$\text{CHCl}_3$ (10)	33	(-) 45
7	MeCN (10)	>99	(-) 54

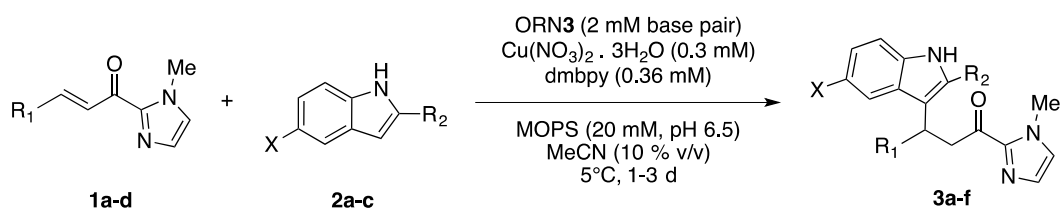
<sup>a</sup>Determined by chiral SFC analysis.

- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM),  $[\text{Cu}(\text{dmbpy})(\text{NO}_3)_2]$  (0.3 mM), MOPS (20 mM, pH 6.5, 600  $\mu\text{L}$ ) and DMSO as a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 9:91 and an enantiomeric excess of (–) 30% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_{\text{R}} = 5.77$  min; minor enantiomer  $t_{\text{R}} = 8.76$  min].

- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and DMF as a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (–) 30% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 5.72 min; minor enantiomer t<sub>R</sub> = 8.67 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and 1,4-dioxane as a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (–) 30% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 5.71 min; minor enantiomer t<sub>R</sub> = 8.66 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and acetone as a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (–) 42% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 5.72 min; minor enantiomer t<sub>R</sub> = 8.66 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and EtOH as a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 0:100 and an enantiomeric excess of (–) 32% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 5.71 min; minor enantiomer t<sub>R</sub> = 8.64 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and EtOH as a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 67:33 and an enantiomeric excess of (–) 45% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 5.72 min; minor enantiomer t<sub>R</sub> = 8.64 min].

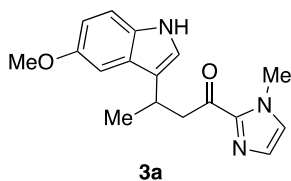
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and CHCl<sub>3</sub> as a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 67:33 and an enantiomeric excess of (–) 45% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 5.72 min; minor enantiomer t<sub>R</sub> = 8.64 min].
- **Following the general procedure F.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and MeCN a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 1:99 and an enantiomeric excess of (–) 54% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 6.25 min; minor enantiomer t<sub>R</sub> = 9.34 min].

#### General Procedure H. Enantioselective Friedel-Crafts alkylations



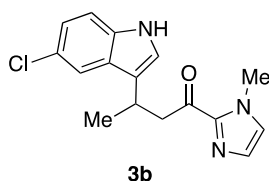
To a 6 mM base pair solution of L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) in MOPS buffer (20 mM, pH 6.5) (200 μL) was added the co-solvent (MeCN 10 % v/v) stock solution (200 μL) and the 0.9 mM solution of [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] in MOPS buffer (20 mM, pH 6.5) (200 μL). The resulting solution (2 mM base pair, 600 μL) was cooled to 5 °C. To the cold mixture was added a 0.5 M solution of enone in MeCN (1.2 μL), followed by a 2.5 M solution of substituted indole in MeCN (1.2 μL). The reaction was mixed by inversion at 5 °C in a cold room. After 1-3 d, the mixture was warmed to rt and extracted with Et<sub>2</sub>O (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over Na<sub>2</sub>SO<sub>4</sub> to give the crude product which was subjected to SFC analysis without further purification.

- **3-(5-Methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (3a)**



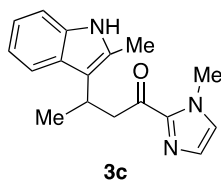
**Following the general procedure H.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and MeCN a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 1:99 and an enantiomeric excess of (–) 54% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 6.25 min; minor enantiomer t<sub>R</sub> = 9.34 min].

- **3-(5-Chloro-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (3b)**



**Following the general procedure H.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 5-chloroindole **2b** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and MeCN a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3b** of 1:99 and an enantiomeric excess of (–) 54% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 5.78 min; minor enantiomer t<sub>R</sub> = 6.88 min].

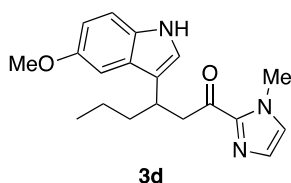
- **3-(1-Methyl-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (3c)**



**Following the general procedure H.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1a** (1 mM), 1-methylindole **2c** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM,

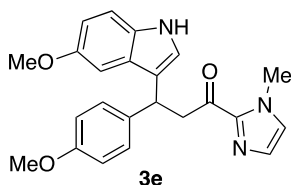
pH 6.5, 600  $\mu$ L) and MeCN a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1a** and **3c** of 1:99 and an enantiomeric excess of (-) 30% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 3.99 min; minor enantiomer  $t_R$  = 5.24 min].

- **3-(5-Methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)hexan-1-one (3d)**



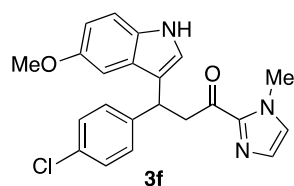
**Following the general procedure H.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1b** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600  $\mu$ L) and MeCN a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1b** and **3d** of 1:99 and an enantiomeric excess of (-) 38% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 12% MeOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 5.63 min; minor enantiomer  $t_R$  = 7.03 min].

- **3-(5-Methoxy-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1(1-methyl-1*H*-imidazol-2-yl)propan-1-one (3e)**



**Following the general procedure H.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1c** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600  $\mu$ L) and MeCN a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1c** and **3e** of 7:93 and an enantiomeric excess of (-) 10% [DAICEL AD-H column; 100 bar; flow: 6.0 mL/min; 30% *i*-PrOH;  $\lambda$  = 220 nm; major enantiomer  $t_R$  = 4.14 min; minor enantiomer  $t_R$  = 6.73 min].

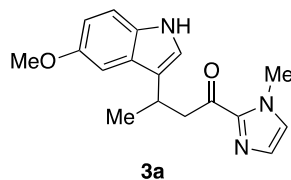
- **3-(5-Methoxy-1*H*-indol-3-yl)-1-(4-chlorophenyl)-1(1-methyl-1*H*-imidazol-2-yl)propan-1-one (3f)**



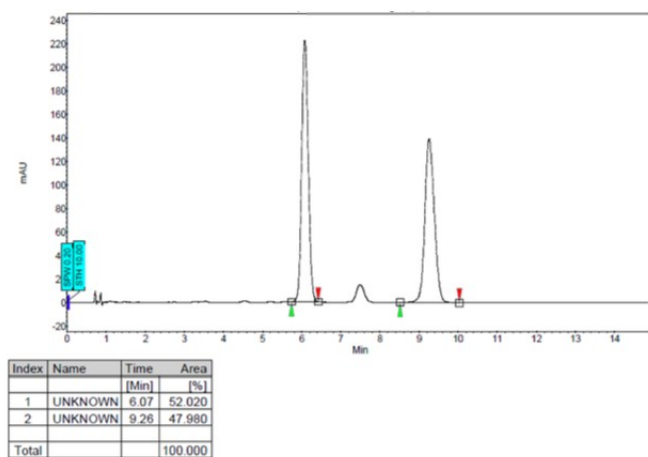
**Following the general procedure H.** L-5'-(CAGUCAGUACUGACUG)<sub>2</sub> (**ORN3**) (2 mM base pair), **1d** (1 mM), 5-methoxyindole **2a** (5 mM), [Cu(dmbpy)(NO<sub>3</sub>)<sub>2</sub>] (0.3 mM), MOPS (20 mM, pH 6.5, 600 μL) and MeCN a co-solvent (10 % v/v); 1 d. SFC analysis of the crude residue indicated a ratio between **1b** and **3f** of 30:70 and an enantiomeric excess of (–) 10% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 20% MeOH; λ = 220 nm; major enantiomer t<sub>R</sub> = 7.13 min; minor enantiomer t<sub>R</sub> = 12.72 min].

## Copies of SFC Chromatograms

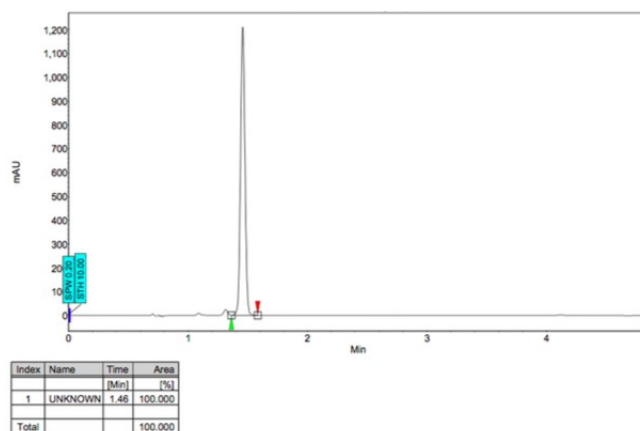
### 3-(5-Methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (3a)



**Racemic (3a)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; first enantiomer  $t_R = 6.07$  min; second enantiomer  $t_R = 9.26$  min].

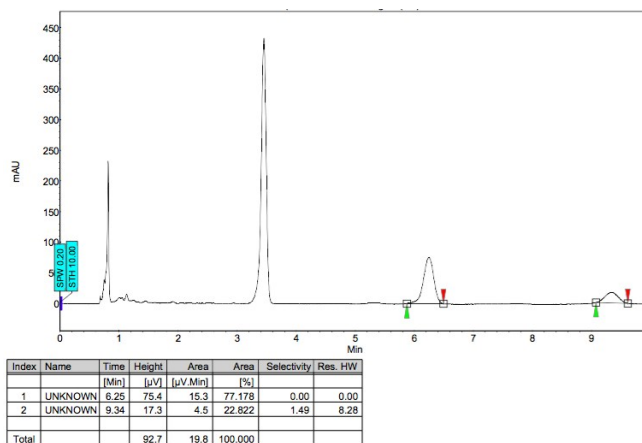


**Starting material (1a)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm;  $t_R = 1.46$  min].

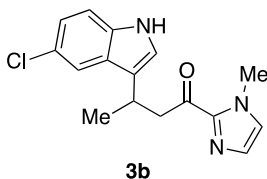




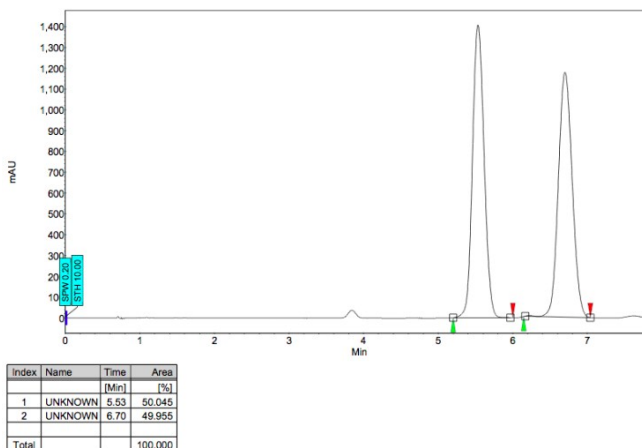
**Following the general procedure H.** SFC analysis of the crude residue indicated a ratio between **1a** and **3a** of 1:99 and an enantiomeric excess of (–) 54% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 6.25$  min; minor enantiomer  $t_R = 9.34$  min].



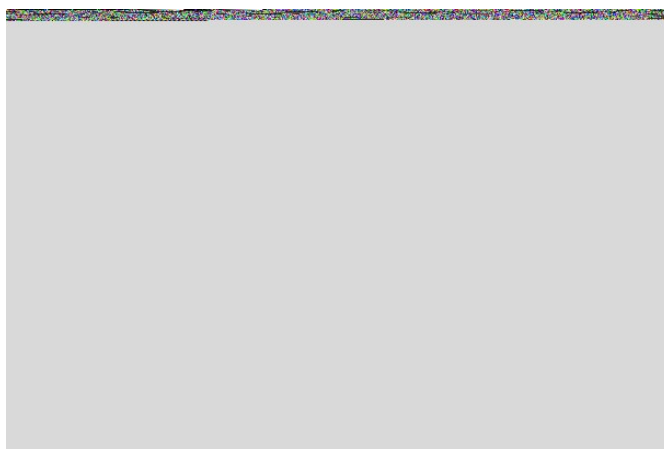
### 3-(5-Chloro-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (**3b**)



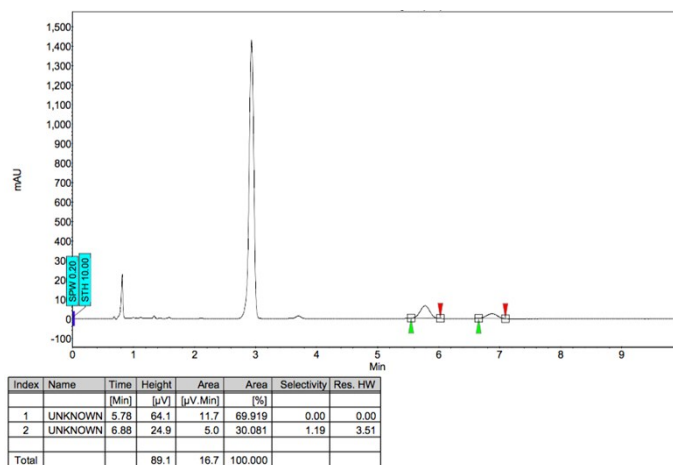
**Racemic (3b)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; first enantiomer  $t_R = 6.07$  min; second enantiomer  $t_R = 9.26$  min].



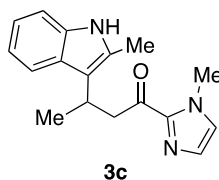
**Starting material (1e)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm;  $t_R = 1.46$  min].



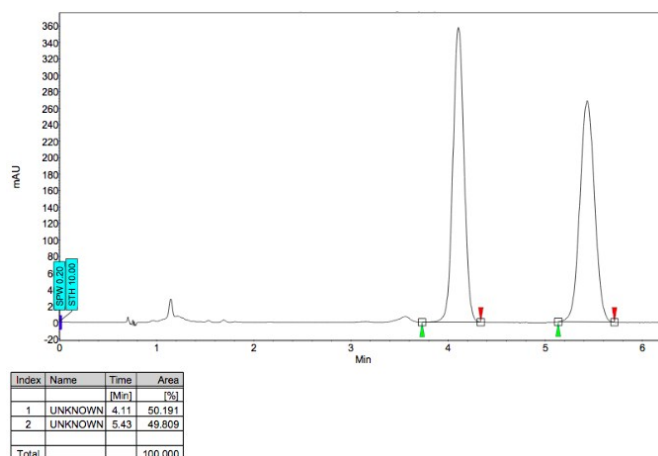
**Following the general procedure H.** SFC analysis of the crude residue indicated a ratio between **1a** and **3b** of 1:99 and an enantiomeric excess of (-) 40% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 5.78$  min; minor enantiomer  $t_R = 6.88$  min].



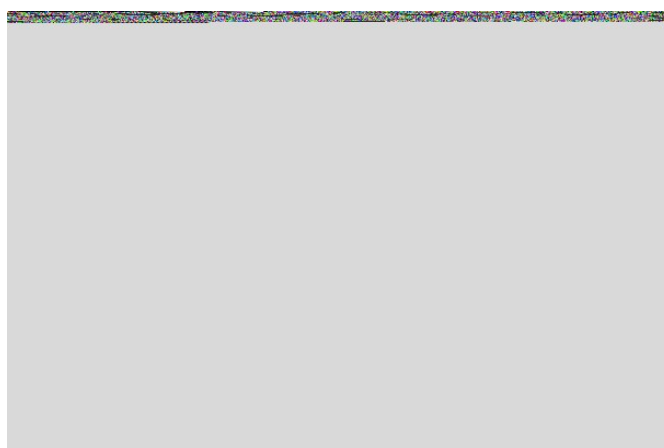
### 3-(1-Methyl-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)butan-1-one (**3c**)



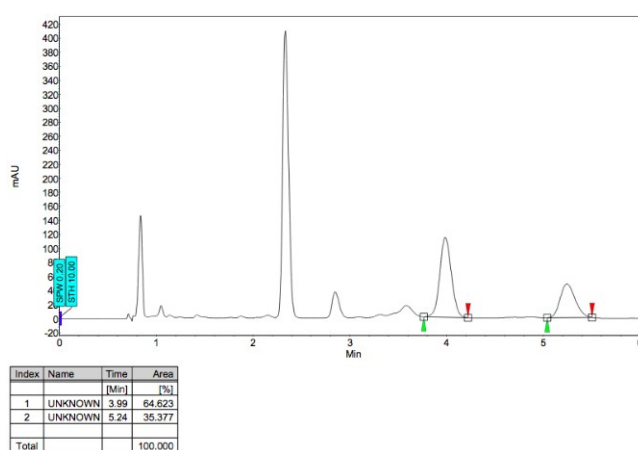
**Racemic (3b)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; first enantiomer  $t_R = 4.11$  min; second enantiomer  $t_R = 5.43$  min].



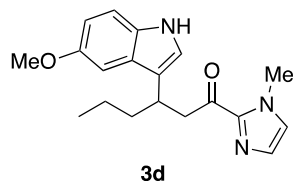
**Starting material (1a)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm;  $t_R = 1.46$  min].



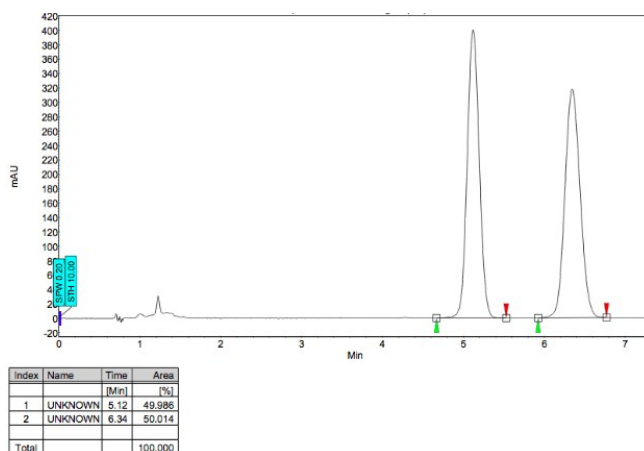
**Following the general procedure H.** SFC analysis of the crude residue indicated a ratio between **1a** and **3c** of 1:99 and an enantiomeric excess of (–) 30% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 3.99$  min; minor enantiomer  $t_R = 5.24$  min].



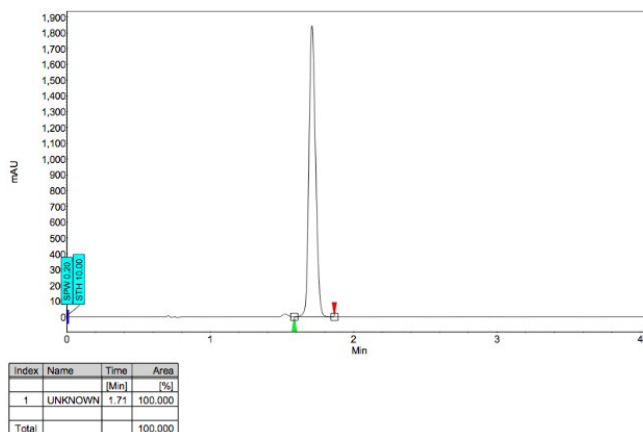
### 3-(5-Methoxy-1*H*-indol-3-yl)-1-(1-methyl-1*H*-imidazol-2-yl)hexan-1-one (**3d**)



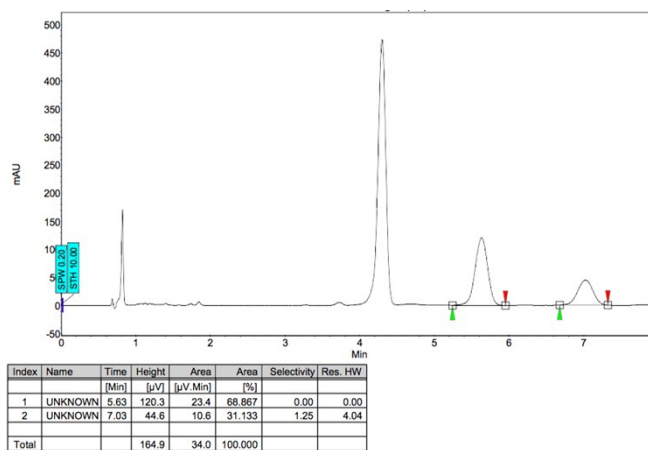
**Racemic (3d)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 12% MeOH;  $\lambda = 220$  nm; first enantiomer  $t_R = 4.11$  min; second enantiomer  $t_R = 5.43$  min].



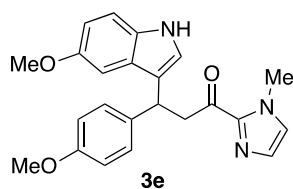
**Starting material (1a)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 15% MeOH;  $\lambda = 220$  nm;  $t_R = 1.71$  min].



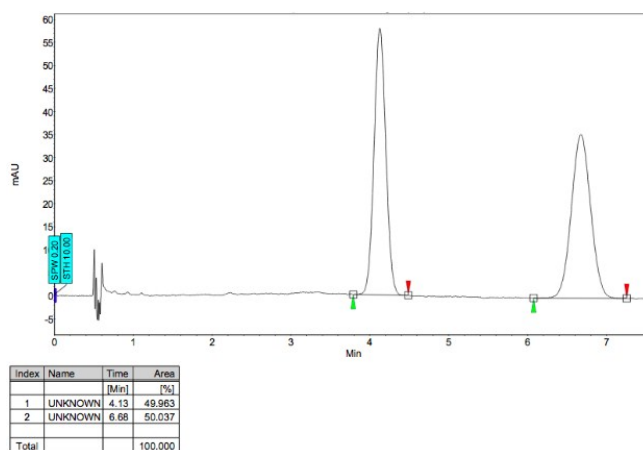
**Following the general procedure H.** SFC analysis of the crude residue indicated a ratio between **1b** and **3d** of 1:99 and an enantiomeric excess of (–) 38% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 12% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 5.63$  min; minor enantiomer  $t_R = 7.03$  min].



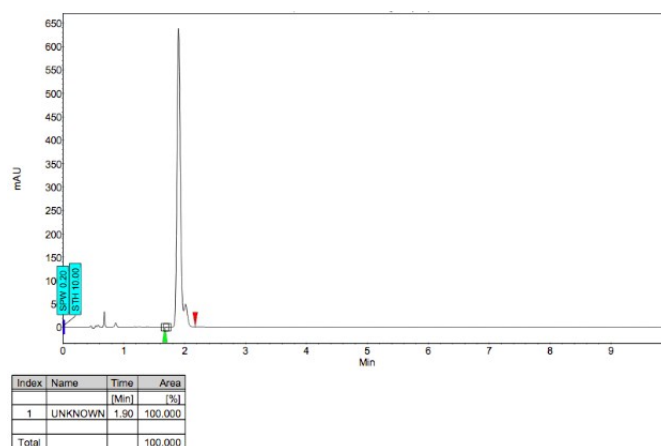
**3-(5-Methoxy-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-1(1-methyl-1*H*-imidazol-2-yl)propan-1-one (3e)**



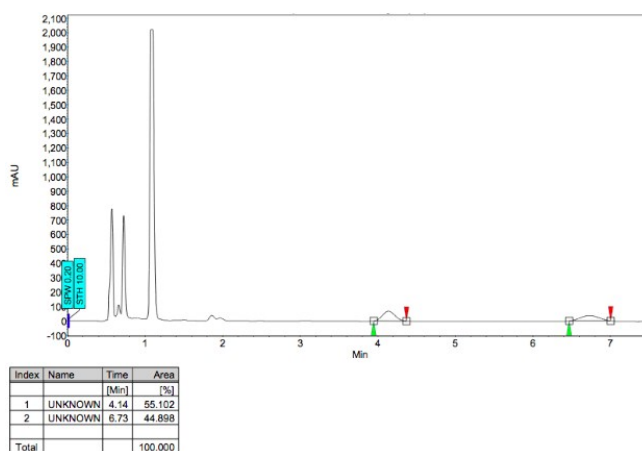
**Racemic (3e)** [DAICEL AD-H column; 100 bar; flow: 6.0 mL/min; 30% *i*-PrOH;  $\lambda = 220$  nm; first enantiomer  $t_R = 4.13$  min; second enantiomer  $t_R = 6.68$  min].



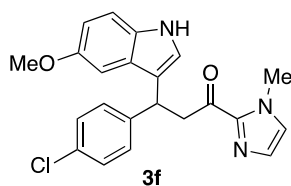
**Starting material (1c)** [DAICEL AD-H column; 100 bar; flow: 6.0 mL/min; 30% *i*-PrOH;  $\lambda = 220$  nm;  $t_R = 1.71$  min].



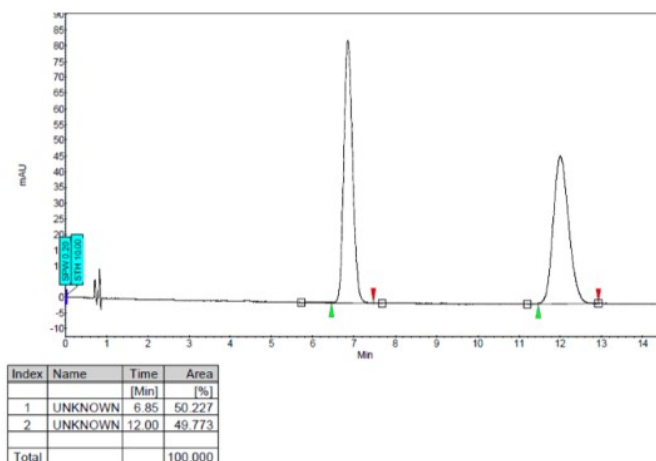
**Following the general procedure H.** SFC analysis of the crude residue indicated a ratio between **1c** and **3e** of 7:93 and an enantiomeric excess of (–) 10% [DAICEL AD-H column; 100 bar; flow: 6.0 mL/min; 30% *i*-PrOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 4.14$  min; minor enantiomer  $t_R = 6.73$  min].



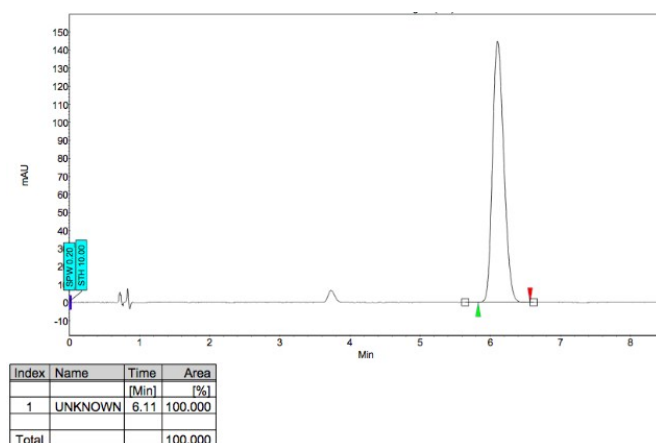
**3-(5-Methoxy-1*H*-indol-3-yl)-1-(4-chlorophenyl)-1(1-methyl-1*H*-imidazol-2-yl)propan-1-one (3f)**



**Racemic (3f)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 20% MeOH;  $\lambda = 220$  nm; first enantiomer  $t_R = 4.13$  min; second enantiomer  $t_R = 6.68$  min].



**Starting material (1d)** [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 20% MeOH;  $\lambda = 220$  nm;  $t_R = 6.11$  min].



**Following the general procedure H.** SFC analysis of the crude residue indicated a ratio between **1b** and **3f** of 30:70 and an enantiomeric excess of (-) 10% [DAICEL AD-H column; 100 bar; flow: 4.0 mL/min; 20% MeOH;  $\lambda = 220$  nm; major enantiomer  $t_R = 7.13$  min; minor enantiomer  $t_R = 12.52$  min].

