Electronic Supplementary Material (ESI) for Photochemical & Photobiological Science

Supporting Information (15 pages)

Enantiospecific photochemical 6π-ring closure of α-substituted atropisomeric acrylanilides – Role of alkali metal ions

Anoklase Jean-Luc Ayitou,[a§] Anthony Clay,[a§] Elango Kumarasamy,[a] Steffen Jockusch,[b] and J. Sivaguru*[,a]

[a] *Department of Chemistry and Biochemistry, North Dakota State University, Fargo, ND 58108-6050. USA.*

[b] *Department of Chemistry, Columbia University, New York, NY 10027. USA.*

e-Mail: sivaguru.jayaraman@ndsu.edu

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1. GENERAL METHODS

All commercially obtained reagents/solvents were used as received; chemicals were purchased from Alfa Aesar®, Sigma-Aldrich®, Acros organics®, TCI America®, Mallinckrodt®, and Oakwood® Products, and were used as received without further purification. Spectrophotometric grade solvents (ethanol and methylcyclohexanes) were purchased from Sigma-Aldrich® and used without further purification for emission measurements. Unless stated otherwise, reactions were conducted in oven-dried glassware under nitrogen atmosphere. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian 400 MHz (100 MHz for ^{13}C) and on 500 MHz (125 MHz for ^{13}C) spectrometers. Data from the ^{1}H-NMR spectroscopy are reported as chemical shift (δ ppm) with the corresponding integration values. Coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), b (broad), d (doublet), t (triplet), q (quartet), m (multiplet) and virt (virtual). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). High-resolution mass spectrum data in Electrospray Ionization mode were recorded on a Bruker – Daltronics® BioTof mass spectrometer in positive (ESI+) ion mode. HPLC analyses were performed on Waters® HPLC equipped with 2525 pump or on Dionex® Ultimate 3000 HPLC. Waters® 2767 sample manager was used for automated sample injection on Waters® HPLC or Ultimate 3000 sample injector was used for injection on Dionex® HPLC. All HPLC injections on Waters® HPLC were monitored using a Waters® 2487 dual wavelength absorbance detector at 254 and 270 nm or on Dionex®. HPLC were monitored using a diode array detector (DAD3000125). Analytical and semi-preparative injections were performed on chiral stationary phase using various columns as indicated below.

i) Regis® PIRKLE COVALENT (*R*,*R*) WHELK–01
   a) 25 cm x 4.6 mm column for analytical injections.
   b) 25 cm x 10 mm column for semi-preparative injections.

ii) CHIRAPAK® AD-H
   a) 0.46 cm x 25 cm column for analytical injections.
   b) 10 mm x 25 cm column for semi-preparative injections.

Masslynx software version 4.1 was used to monitor/analyze the HPLC injections on Waters® and to process HPLC traces. Chromeleon 7 software was used to monitor and process HPLC injections on Dionex® HPLC. Igor Pro® Software version 6.0 was used to process the HPLC graphics. UV-Vis spectra were recorded on Shimadzu 2501PC UV-Vis spectrometer using UV quality fluorimeter cells (with range until 190 nm) purchased from Luzchem. Optical

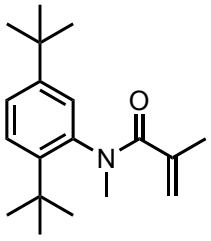
activity values were recorded on JASCO® DIP – 370 digital polarimeter. CD spectra were recorded on JASCO® J-815 with JASCOPTC-423S/15 temperature controller maintained by liquid nitrogen. When necessary, the compounds were purified by combiflash equipped with dual wavelength UV-Vis absorbance detector (Teledyn ISCO) using hexanes:ethyl acetate as the mobile phase and Redisep® cartridge filled with silica (Teledyne ISCO) as stationary phase. In some cases, compounds were purified by column chromatography on silica gel (Sorbent Technologies®, silica gel standard grade: porosity 60 Å, particle size: 230 x 400 mesh, surface area: 500 – 600 m^2/g, bulk density: 0.4 g/mL, pH range: 6.5 – 7.5). Unless indicated, the Retardation Factor (R*f*) values were recorded using a 5-50% hexanes:ethyl acetate as mobile phase and on Sorbent Technologies®, silica Gel TLC plates (200 mm thickness w/UV_{254}).

Photophysical Methods.

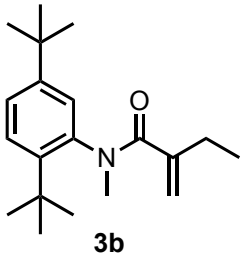
Spectrophotometric solvents (Sigma-Aldrich®) were used when ever necessary unless or otherwise mentioned. UV quality fluorimeter cells (with range until 190 nm) were purchased from Luzchem®. Absorbance measurements were performed using a Shimadzu® UV-2501PC UV-Vis spectrophotometer. Emission spectra were recorded on a Horiba Scientific® Fluorolog 3 spectrometer (FL3-22) equipped with double-grating monochromators, dual lamp housing containing a 450-watt CW xenon lamp and a UV xenon flash lamp (FL-1040), Fluorohub/MCA/MCS electronics and R928 PMT detector. Emission and excitation spectra were corrected in all the cases for source intensity (lamp and grating) and emission spectral response (detector and grating) by standard instrument correction provided in the instrument software. Fluorescence emission spectra were processed by FluorEssence® software. Fluorescence lifetimes were determined by time correlated single photon counting using a pulsed diode (NanoLED) emitting at 263 nm and processed using DAS6® V6.4 software. The goodness-of-fit was assessed by minimizing the reduced chi squared function and further judged by the symmetrical distribution of the residuals.

2. CHART AND SYNTHETIC PROTOCOLS

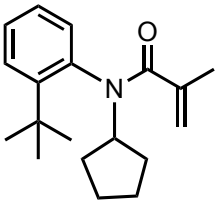
2.1 Chart



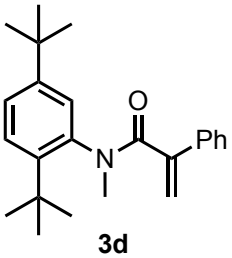
3a



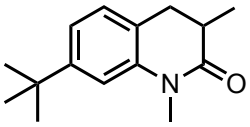
3b



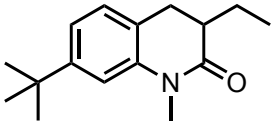
3c



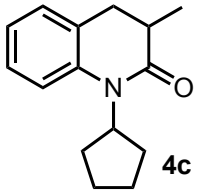
3d



4a



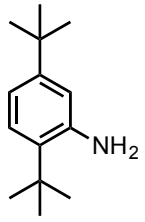
4b



4c

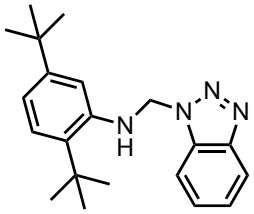
Note: The synthesis and characterization of α-substituted acrylanilides **3a-d** and its 3,4-dihydro-2-quinolin-2-one photoproducts **4a-c** were previously reported.[1-4]

2.2 Synthetic protocols for α-substituted acrylanilides **3b** and **3d**.



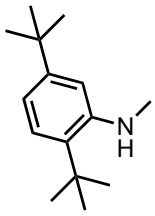
5

HCHO
1-H-benzotriazole
MeOH, rt, 16-20 h



6

$NaBH_4$
THF, 0 °C to rt, 12 h



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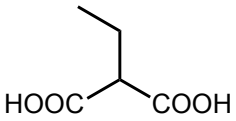
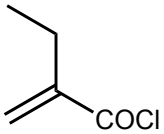
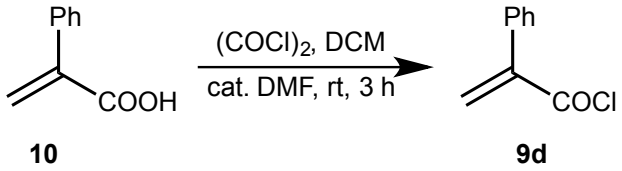


8

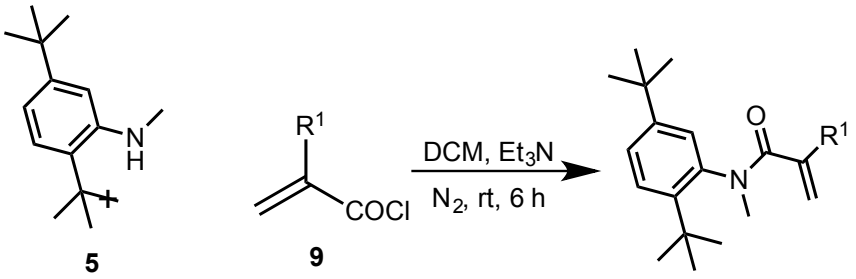
1. Et_2NH, 5-10 °C
(HCHO)n, reflux, 2 h
2. $SOCl_2$, 50 °C, 5 h



9b



10 **9d**

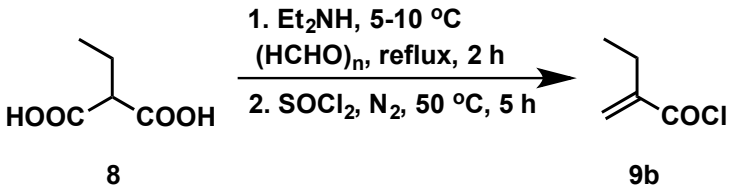


5 **9**

3b = R^3 = Et
3d = R^3 = Ph

3. SYNTHESIS AND CHARACTERIZATION OF **3b** AND **3d**

3.1 Synthesis of acid chloride derivatives **9b** and **9d**

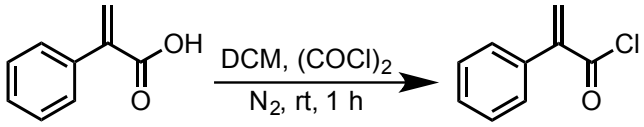


8 **9b**

Scheme S1: Synthesis of 2-methylenebutanoyl chloride **9b**

2-Methylenebutanoyl chloride was synthesized according to a procedure reported in the literature.[5] To a solution of ethyl malonic acid (1.85 g, 1.0 equiv) in dry ethyl acetate (40 mL) at 0 ^{o}C under N_2 atmosphere diethylamine (2.17 mL, 1.5 equiv) was added. The mixture was stirred for 5 min followed by the addition of paraformaldehyde (0.67 g, 1.5 equiv) in 2 portions. The resulting mixture was stirred for 5 mins and then moved to an oil bath where it was refluxed for 2 h. The mixture was cooled to room temperature and quenched with water. The pH of the solution was adjusted to 1 by carefully adding c*onc.* HCl and extracted with ethyl acetate (3 X 15 mL). The combined organic layer was dried over *anhyd.* Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield crude product as a pale yellow oil. The crude product was directly taken to the next stage without further purification.

To the crude product under N_2 atmosphere thionyl chloride (1.54 mL, 1.0 equiv) was added with stirring. The mixture was heated to 50 ^{o}C and maintained for 3 h. After 3 h, the excess thionyl chloride was removed under reduced pressure while the temperature was maintained at 25 ^{o}C. The vacuum was released under N_2 and the residue was taken up in dichloromethane (DCM) and directly taken to next step without further analysis or purification.



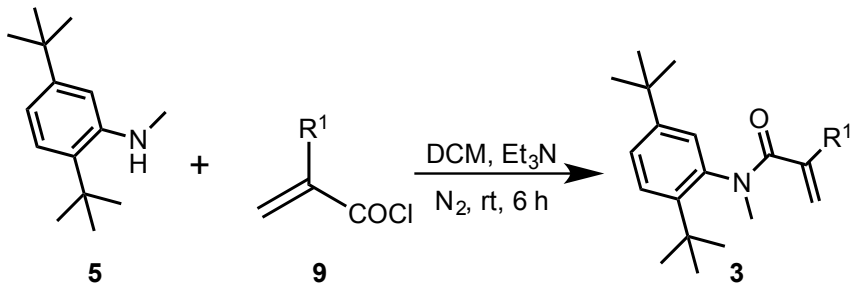
10 **9d**

Scheme S2: Synthesis of atopic acid chloride **9d**

To a solution of atopic acid **10** (1.1 g, 7.33 mmol, 1.0 equiv) in DCM (10 mL) at room temperature added two drops of DMF (catalytic). To this solution oxalyl chloride (2.5 equiv) was slowly added during which white effervescence was observed. The mixture was further stirred for 1 h and the solvent and excess oxalyl chloride was removed under reduced pressure while

the temperature was maintained at 25 °C. The vacuum was released under N_2 and the residue was taken up in DCM and directly taken to next step without further analysis or purification.

3.2 Synthesis of atropisomeric α-substituted acrylanilide **9b** and **9d**



5 **9** **3**

b = R^1 = Et

d = R^1 = Ph

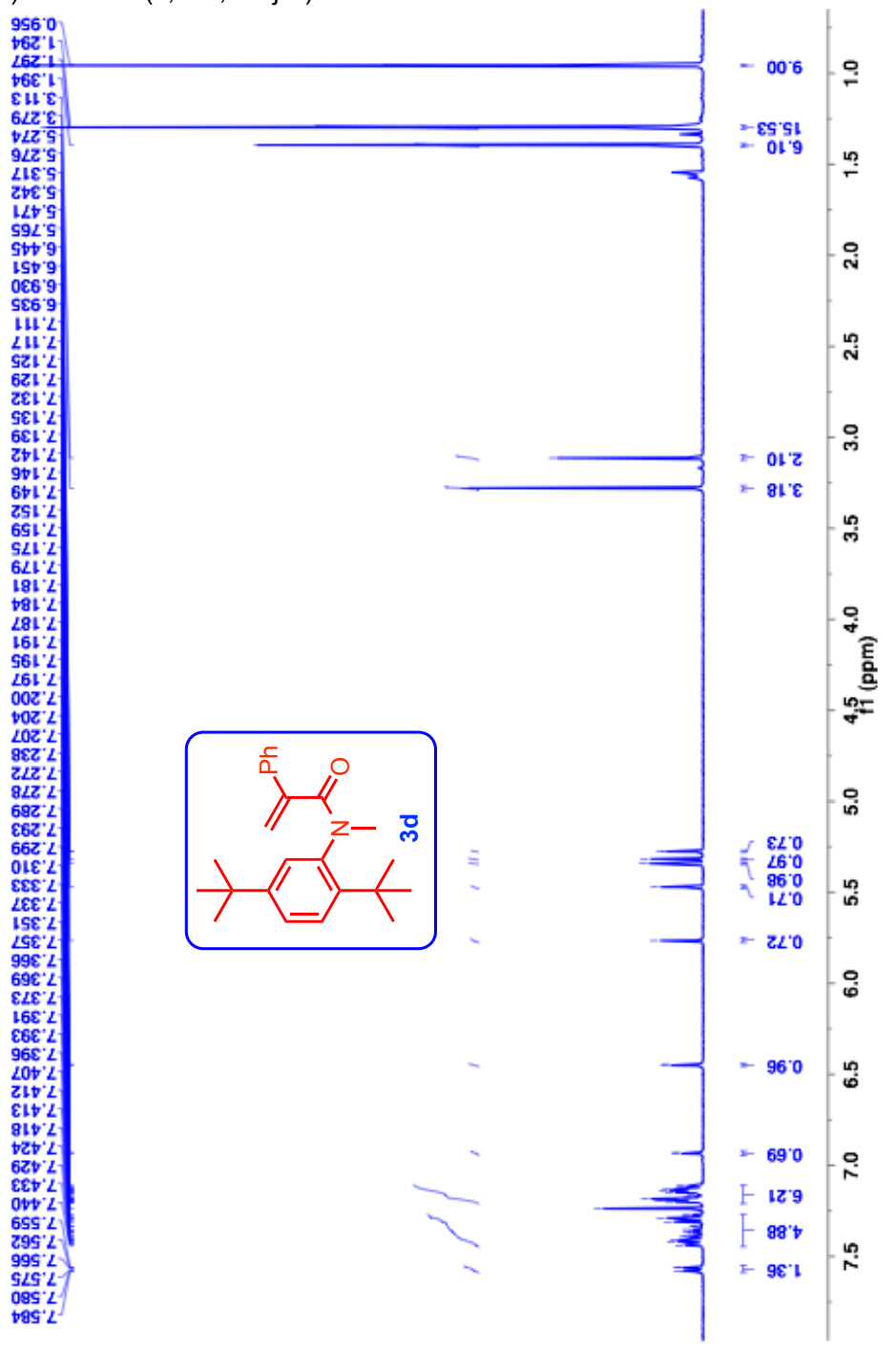
Scheme S3: Synthesis of atropisomeric α-substituted acrylanilide **3b** and **3d**

To a solution of N-Methyl aniline derivative **5** (1.0 g, 1.0 equiv), triethylamine (2.0 equiv) in dry DCM (15 mL) at 0 °C under N_2 atmosphere corresponding acyl chloride **9** (1.1 equiv) was added. The resulting solution was slowly allowed to warm to room temperature over 6 h. After the reaction, water was added, stirred and the layers were separated. The organic layer was washed with DM water (2 X 15 mL), dried over *anhyd.* Na_2SO_4, filtered and the solvent was removed under reduced pressure to yield crude product. The crude product was purified by combiflash using hexanes:ethyl acetate mixture.

The yield for **3b** and **3d** was around 70% and 90% respectively.

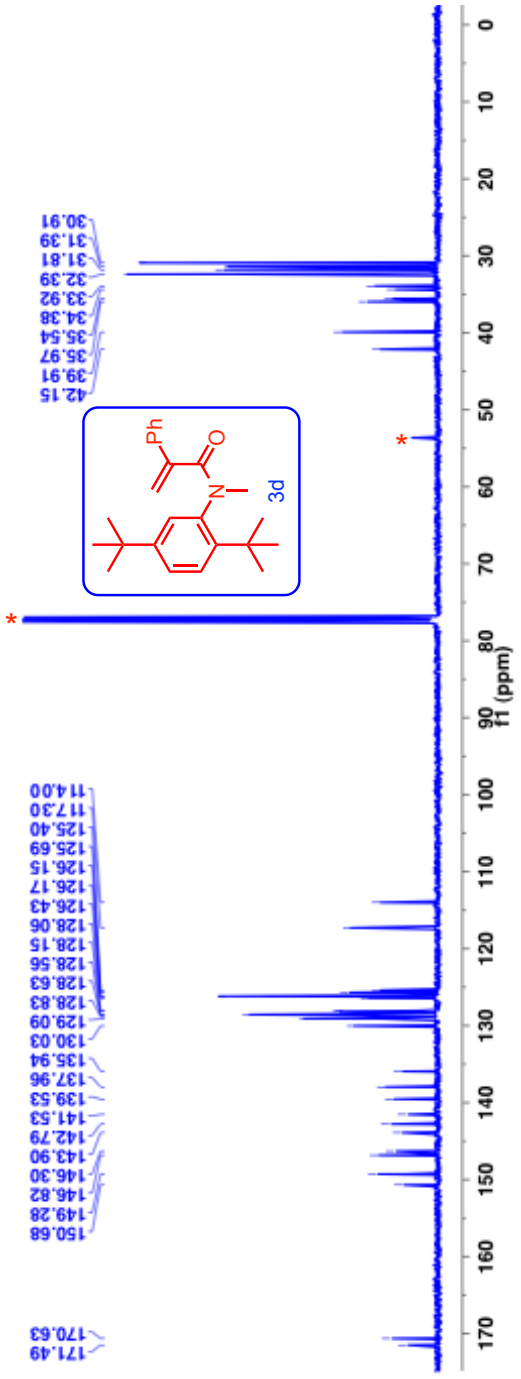
3.3 Characterization of α-substituted acrylanilide **3d**

[1]H-NMR (400 MHz, $CDCl_3$ δ ppm): 7.58-7.55 (m, 2H, minor), 7.44-7.27 (m, 5H, major+minor), 7.21-7.11 (m, 6H, major+minor), 6.93 (d, *J* = 2 Hz, 1H, minor), 6.45 (d, *J* = 1.6 Hz, 1H, major), 5.76 (s, 1H, minor), 5.47 (s, 1H, minor), 5.34 (s, 1H, major), 5.32 (s, 1H, major), 5.28-5.27 (m, 1H, minor), 3.28 (s, 3H, major), 3.11 (s, 2H, minor), 1.39 (s, 6H, minor), 1.297-1.29 (m, 15H, major+minor) and 0.96 (s, 9H, major).



Note: The compound appears as a mixture of major:minor rotamers in the ratio 3:2

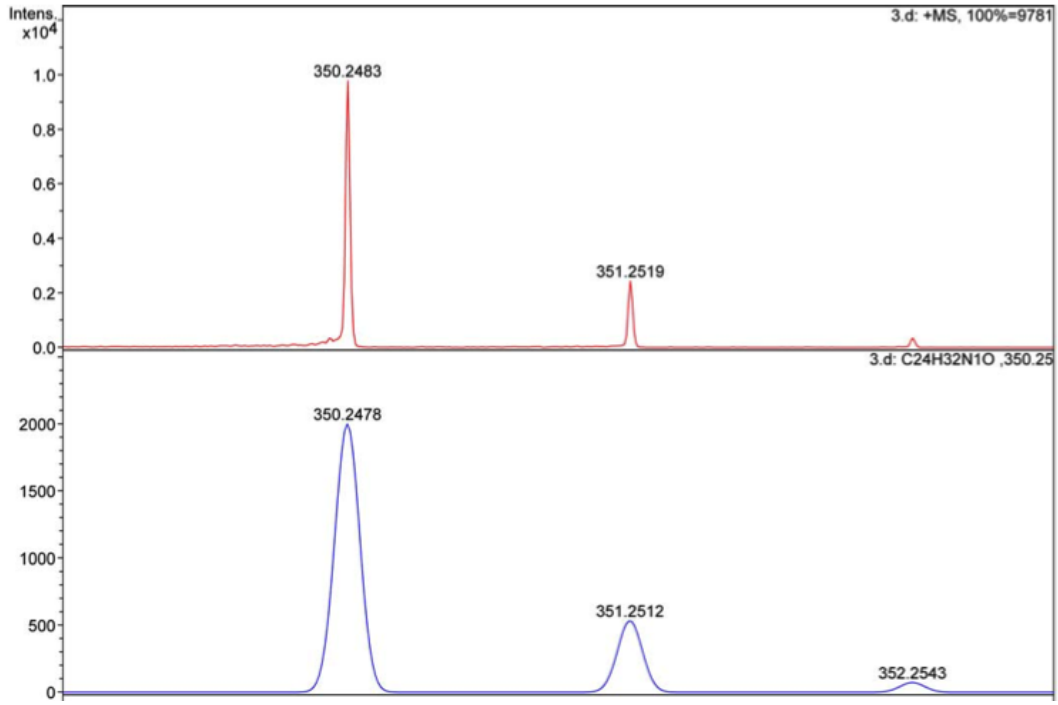
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 171.5, 170.6, 150.7, 149.3, 146.8, 146.3, 143.9, 142.8, 141.5, 139.5, 137.96, 135.94, 130.0, 129.1, 128.8, 128.63, 128.56, 128.2, 128.1, 126.4, 126.2, 126.1, 125.7, 125.4, 117.3, 114.0, 42.2, 39.9, 35.97, 35.5, 34.4, 33.9, 32.4, 31.8, 31.4 and 30.9



* = Solvent

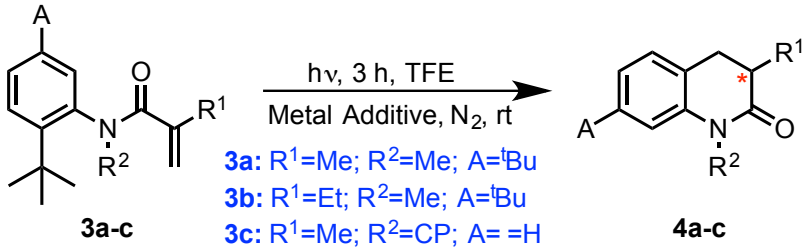
Note: The compound appears as a mixture of major:minor rotamers.

HRMS-ESI (m/z) ([M+ Na]+):
Calculated : 350.2478
Observed : 350.2483
Δm : 1.4 ppm



4. General irradiation procedures and characterization of photoproducts

4.1 Process for photoreaction of **3a-c**

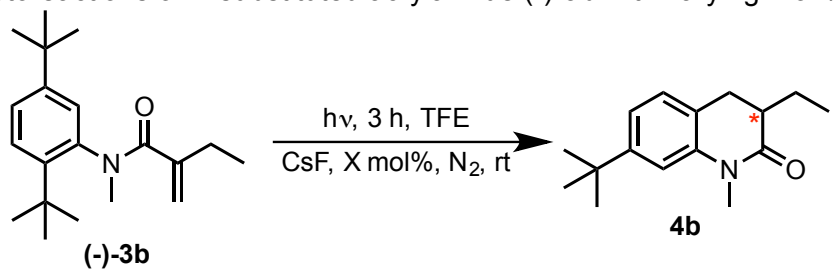


Scheme S4: Photoreaction of α-substituted acrylanilides derivatives **3a-c.**

Stock solution of 2,2,2,-trifluoroethanol (TFE) saturated with various additives were prepared prior (approximately 12 h) to the respective photoreaction. The additive(s) was flame dried while being evacuated under high vacuum. The flame-dried additives were stored under N_2 atmosphere and subsequently dissolved in TFE. The resulting solution was passed through a microfilter and was added to optically pure atropisomeric α-substituted acrylanilides **3a-c.** If a turbid solution was observed it was again passed a microfilter to obtain a transparent solution. The resulting solution was irradiated at 25 °C for 3 h in Pyrex test tube with a 450 W medium pressure mercury lamp placed inside a water cooled quartz well under constant flow of nitrogen.

After irradiation, the solvent was evaporated under reduced pressure, dissolved in DCM and filtered through a cotton plug. The solution was concentrated and the residue was analyzed on a chiral stationary phase on a HPLC to ascertain the enantiomeric excess in the photoproduct.

4.2 General photoreactions of α-substituted acrylanilide (-)-**3b** with varying mol % of CsF.



(-)-3b **4b**

Scheme S5: Photoreaction of α-substituted acrylanilide **3b** with varying CsF mol%**.**

A stock solution of CsF in TFE (71.6 mg in 25 mL of TFE) was prepared by adding TFE into the flame dried CsF. This solution was allowed to stir overnight prior to use in a sealed flask under nitrogen atmosphere. The necessary amount of CsF (from a stock solution in CsF in TFE) was then added to optically pure (-)-**3b** followed by the addition of TFE. The resulting turbid solution was then sonicated for an hour. In some cases, the solution was turbid even after sonication. In those scenario the turbid solution was employed as such for the photoreaction. The samples were irradiated for 3 h at ambient temperatures in a Pyrex test tube with a 450 W medium pressure mercury lamp placed inside a water cooled quartz well under constant flow of nitrogen. After irradiation, the solvent was evaporated under reduced pressure, dissolved in DCM and filtered through a cotton plug. The solution was concentrated and the residue was analyzed on a chiral stationary phase on a HPLC to ascertain the enantiomeric excess in the photoproduct (Table S1).

Table SI: Photoreaction of α-substituted acrylanilide **3b** in TFE with varying mol% of CsF**.**[a]

Entry	Substrate	CsF (mol%)	%ee [b]
1)	(-)-**3b**	10	15 (B)
2)		50	50 (B)
3)		100	54 (B)
4)		500	69 (B)

[a] values are an average of a minimum of 3 trials with an average of ±5% error. [b] "(B)" represents the second enantiomer that elutes out during chiral stationary phase separation on a HPLC.

4.3 HPLC separation and analysis conditions for **3a-c** and **4a-c**.

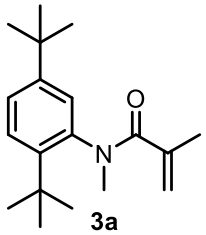
(-) and (+) are assigned based on the sign of CD spectra at 285 nm in methylcyclohexane (MCH) for **3a** and **3b**, and MeOH for **3c**. Peak-A (pkA) and peak-B (pkB) refers to the elution order for a given pair of enantiomers on a chiral stationary phase.

HPLC separation conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 3 mL/min

Retention time (min): (-)-**3a** ~49.55 and (+)-**3a** ~51.22



3a

HPLC analysis conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 1 mL/min

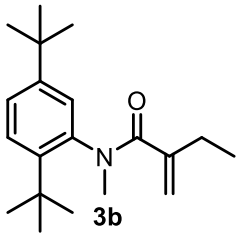
Retention time (min): (-)-**3a** ~47.50 and (+)-**3a** ~53.82

HPLC separation conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 4 mL/min

Retention time (min): (-)-**3b** ~30.72 and (+)-**3b** ~40.52



3b

HPLC analysis conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 1 mL/min

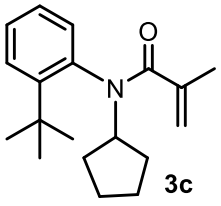
Retention time (min): (-)-**3b** ~36.85 and (+)-**3b** ~45.57

HPLC separation conditions

Column: AD-H; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 3 mL/min

Retention time (min): (+)-**3c** ~13.42 and (-)-**3c** ~18.73



3c

HPLC analysis conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 1 mL/min

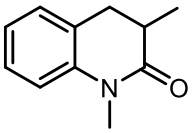
Retention time (min): (+)-**3c:** ~47.62 and (-)-**3c:** ~67.7

HPLC analysis conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 1 mL/min

Retention time (min): **4a**: ~ 33.55 and *ent*-**4a**: ~ 35.36



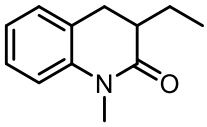
4a

HPLC analysis conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 1 mL/min

Retention time (min): **4b**: ~29.50 and *ent*-**4b**: ~37.85



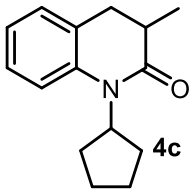
4b

HPLC analysis conditions

Column: (R,R) WHELK-O1; Abs. detector: 254 nm and 270 nm

Mobile phase: Hexanes:IPA= 98:2; Flow rate: 1 mL/min

Retention time (min): **4c**: ~14.80 and *ent*-**4c**: ~ 20.00



4c

5. PHOTOPHYSICAL MEASUREMENTS OF **3a** AND **3d**

5.1 Fluorescence and fluorescence lifetime measurement of **3a** and **3d**

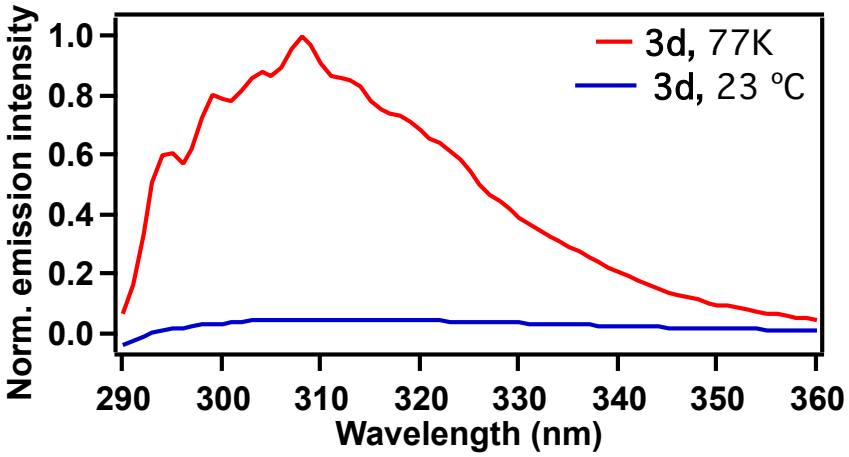


Figure S1: Fluorescence spectra of **3d** in ethanol at 77 K and at 23 °C. ([**3d**] ~ 0.5 mM). λ_{exc} = 280 nm.

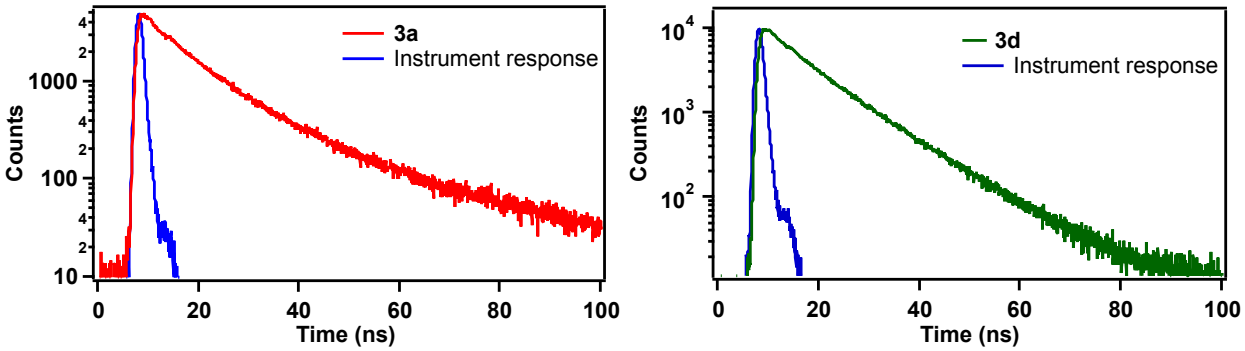


Figure S2: Fluorescence decay traces of **3a** and **3d** in ethanol glass at 77 K after pulsed excitation at 263 nm monitored at 310 nm ([**3a**] ~ 2.0 mM and ([**3d**] ~ 0.5 mM). Instrument response in blue.

5.2 UV-Vis spectra of **3a, d**

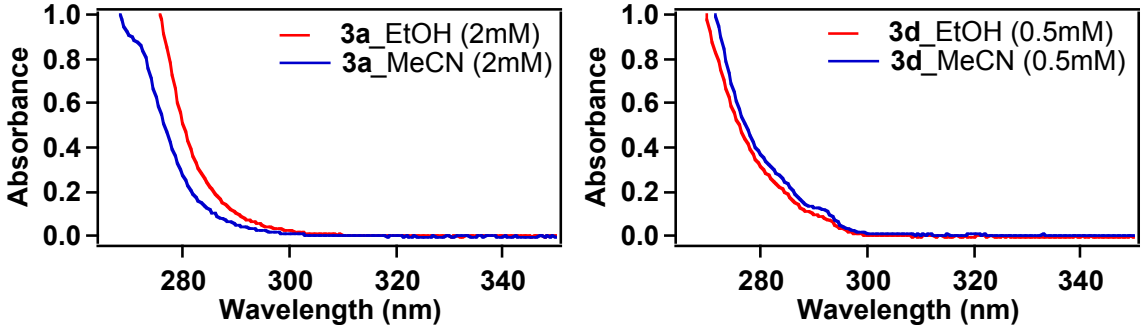


Figure S3: UV-Vis spectra of **3a** (left) and **3d** (right) in ethanol and acetonitrile respectively.

6 REFERENCES

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