Fluorogenic organocatalytic reactions

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Chapter 2

Experimental methods and characterization

In this chapter the general information about the applied apparatus, solvents and chemicals is presented. The synthetic methods of the compounds are explained with details when the synthesized compound or the synthetic procedure is new. Otherwise, a schematic representation of the synthetic procedure is shown.

2.1. General information

Compounds 6,1–3 9,4 15,5,6 and 17,2,3 were synthesized following the literature methods. In some cases we modified the literature procedures.

Catalysts 25,7,8 26,9 27,10 29,11,12 and 35,10 were synthesized following the methods of the literature, in some cases with small modifications. Catalysts 33 and 37 were obtained from Sigma-Aldrich. Catalyst 34 and 36 were synthesized in the synthetic organic chemistry group of the van ‘t Hoff Institute for Molecular Sciences, University of Amsterdam.

2,4-Dimethylpyrrole was purified using distillation freshly before use. Other commercially available reagents were used as purchased.

DCM and DMF were dried by standing over 4 Å activated molecular sieves. THF was dried over sodium wire in the presence of benzophenone. The mixture was refluxed and THF was distilled under inert gas atmosphere and collected.
Flash column chromatography was carried out using silica gel 60A, 0.040-0.063 mm. Commercially available pre-coated TLC plastic sheets (Silica gel 60 F254) were used for thin layer chromatography (TLC). Preparative TLC was carried out using commercially available pre-coated TLC glass plates (PLC Silica gel 60 F254, 1 mm). A UV lamp (254 or 366 nm) was used for visualization. Chiral HPLC was performed using a Shimadzu LC-20AD liquid chromatograph equipped with SPD-M20A diode array detector and chiral OD-H or AD columns. Isopropanol in heptane was used as the eluent. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance 400 spectrometer and analyzed using the MestReNova v 7.1.2 (Mestrelab Research S.L.) software. Signal positions are reported in δ (ppm) with the abbreviations s, d, br and m denoting singlet, doublet, broad and multiplet, respectively. All $^1$H NMR chemical shifts are referenced to SiMe$_3$ as an external standard (0.00 ppm). All $^{13}$C NMR chemical shifts in CDCl$_3$ were referenced to the residual solvent peak at 77.00 ppm but are reported vs. tetramethylsilane. All coupling constants, J, are quoted in Hz. Infra-red spectra were recorded on a Bruker IR spectrometer model α-Platinum ATR using neat solid samples. Optical rotation was measured using Perkin-Elmer 241 polarimeter. Mass spectra were collected on an AccuTOF LC, JMS-T100LP Mass spectrometer (JEOL, Japan). The measurement conditions were as follows: Positive-ion mode; Needle voltage 2000 V, Orifice 1 voltage 90 V, Orifice 2 voltage 9 V, Ring Lens voltage 22 V. Ion source temperature 30 °C, spray temperature -20 °C. Flow injection with a flow rate of 0.01 ml/min. High precision microscope cover glasses (22 × 22 mm) from Marienfeld were used to immobilize the catalysts. A Gilden Photonics Fluorosense-M series spectrometer equipped with two double monochromators was used to follow the Michael reactions. A Bischoff HPLC pump was used to circulate the solution through a 3 mm path length quartz flow cuvette. UV-vis absorption spectra were recorded on a double beam Shimadzu UV-2700 spectrophotometer. A SPEX fluoror 3-22 fluorimeter equipped with double grating monochromators in excitation and emission channels was used to record fluorescence excitation and emission spectra. The spectra were collected in the right angle geometry. A 450 W Xe-lamp was the light source. The detector was a Peltier cooled R636-10 (Hamamatsu) photomultiplier tube. The fluorescence lifetime of the compounds was measured using a home built time-correlated single photon counting setup. The setup consists of a Triapphire laser (Chameleon Ultra, Coherent), optical parametric oscillator (Mira OPO PP-Automatic, Coherent), pulse picker (PulseSelect, APE), dichroic mirror, photodiode, multichannel plate photomultiplier tube (PMT, R3809U-50 or R3809U-51, Hamamatsu), and monochromator (ORIEL Cornerstone 260). A dilute scattering solution (Ludox) was used to measure the instrument response function (IRF) at the excitation wavelength. A home built total internal reflection fluorescence microscope was used to collect the data from reaction mixtures described in chapter 6. The microscope was equipped with a Stabilite 2017 argon ion laser, and a Hamamatsu ORCA-
Flash column chromatography was carried out using silica gel 60A, 0.040-0.063 mm. Commercially available pre-coated TLC plastic sheets (Silica gel 60 F254) were used for thin layer chromatography (TLC). Preparative TLC was carried out using commercially available pre-coated TLC glass plates (PLC Silica gel 60 F254, 1 mm). A UV lamp (254 or 366 nm) was used for visualization. Chiral HPLC was performed using a Shimadzu LC-20AD liquid chromatograph equipped with SPD-M20A diode array detector and chiral OD-H or AD columns. Isopropanol in heptane was used as the eluent. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance 400 spectrometer and analyzed using the MestReNova v 7.1.2 (Mestrelab Research S.L.) software. Signal positions are reported in δ (ppm) with the abbreviations s, d, br and m denoting singlet, doublet, broad and multiplet, respectively. All $^1$H NMR chemical shifts are referenced to SiMe$_3$ as an external standard (0.00 ppm). All $^{13}$C NMR chemical shifts in CDCl$_3$ were referenced to the residual solvent peak at 77.00 ppm but are reported vs. tetramethysilane. All coupling constants, J, are quoted in Hz. Infra-red spectra were recorded on a Bruker IR spectrometer model a-Platinum ATR using neat solid samples. Optical rotation was measured using Perkin-Elmer 241 polarimeter. Mass spectra were collected on an AccuTOF LC, JMS-T100LP Mass spectrometer (JEOL, Japan). The measurement conditions were as follows: Positive-ion mode; Needle voltage 2000 V, Orifice 1 voltage 90 V, Orifice 2 voltage 9 V, Ring Lens voltage 22 V. Ion source temperature 30 °C, spray temperature -20 °C. Flow injection with a flow rate of 0.01 ml/min. High precision microscope cover glasses (22 × 22 mm) from Marienfeld were used to immobilize the catalysts. A Gilden Photonics Fluorosense-M series spectrometer equipped with two double monochromators was used to follow the Michael reactions. A Bischoff HPLC pump was used to circulate the solution through a 3 mm path length quartz flow cuvette. UV-vis absorption spectra were recorded on a double beam Shimadzu UV-2700 spectrophotometer. A SPEX fluororolog 3-22 fluorimeter equipped with double grating monochromators in excitation and emission channels was used to record fluorescence excitation and emission spectra. The spectra were collected in the right angle geometry. A 450 W Xe-lamp was the light source. The detector was a Peltier cooled R636-10 (Hamamatsu) photomultiplier tube. The fluorescence lifetime of the compounds was measured using a home built time-correlated single photon counting setup. The setup consists of a Ti:sapphire laser (Chameleoon Ultra, Coherent), optical parametric oscillator (Mira OPO PP-Automatic, Coherent), pulse picker (PulseSelect, APE), dichroic mirror, photodiode, multichannel plate photomultiplier tube (PMT, R3809U-50 or R3809U-51, Hamamatsu), and monochromator (ORIEL Cornerstone 260). A dilute scattering solution (Ludox) was used to measure the instrument response function (IRF) at the excitation wavelength. A home built total internal reflection fluorescence microscope was used to collect the data from reaction mixtures described in chapter 6. The microscope was equipped with a Stabilite 2017 argon ion laser, and a Hamamatsu ORCA-
2.2. Synthesis of the substrate BODIPYS

There are different methods to prepare the BODIPYS.

Method A. From pyrroles and acid chlorides or anhydrides

These chromophores can be synthesized via condensation of acyl chlorides with pyrrole. Other activated carboxylic acid derivatives can also be used in place of acid chlorides.

![Scheme 3. Synthesis of BODIPY dyes via condensation of acid chloride and pyrrole](image)

Method B. From pyrroles and aromatic aldehydes

This method requires an oxidation step. The oxidant is normally p-chloranil or DDQ.

![Scheme 4. Synthesis of the BODIPY via condensation of aldehyde and pyrrole](image)

Method C. From ketopyrroles

This method is suitable to synthesize unsymmetrical BODIPYS.

![Scheme 5. Synthesis of the unsymmetrical BODIPY](image)

2.2.1. Synthesis of compound 6

We reduced terephthalaldehyde following the method of reference 2. In this step slow addition of the reducing agent and the low temperature are determining factors to reduce the by-product resulting from reduction of two aldehyde groups. Compounds 2-5 were synthesized following the methods of reference 3. Compound 5 was oxidized following the method of reference 1. In this reaction, the purity of dimethyl pyrrole is important to decrease the amounts of the by-products. We used freshly distilled dimethyl pyrrole and kept it under inert gas atmosphere before use. Trifluoroacetic acid (TFA) catalyzes the reaction between aldehyde and dimethyl pyrrole and kept it under inert gas atmosphere before use. Trifluoroacetic acid (TFA) catalyzes the reaction between aldehyde and dimethyl pyrrole. On the other hand, it increases the possibility of producing by-products by facilitating the polymerization of dimethyl pyrrole. We noticed that 10 µL of TFA per 1 g of dimethyl pyrrole is the optimum amount of TFA which can be used. Light shielding improves the yield of this reaction by decreasing the possibility of producing the polymerization product. Protecting the hydroxyl group of 1 helped us to produce alcohol 5 in high yield. We followed the method of reference 1 to oxidize alcohol 5 to aldehyde 6. The conditions of the reaction...
Experimental methods and characterizations

Flash4.0 sCMOS camera. The emission light was filtered with notch 488/20 and 496 nm long pass filters.

2.2. Synthesis of the substrate BODIPYs

There are different methods to prepare the BODIPYs.

Method A. From pyrroles and acid chlorides or anhydrides

These chromophores can be synthesized via condensation of acyl chlorides with pyrrole. Other activated carboxylic acid derivatives can also be used in place of acid chlorides.

Method B. From pyrroles and aromatic aldehydes

This method requires an oxidation step. The oxidant is normally p-chloranil or DDQ.

Method C. From ketopyrroles

This method is suitable to synthesize unsymmetrical BODIPYs.

We used method A to prepare compound 8 (Scheme 3; \(R_1 = \text{CH}_3, R_4 = \text{Ph}\)) which does not contain any substitution on the phenyl ring. Other BODIPYs were prepared following method B.

2.2.1. Synthesis of compound 6

We reduced terephthalaldehyde following the method of reference 2. In this step slow addition of the reducing agent and the low temperature are determining factors to reduce the by-product resulting from reduction of two aldehyde groups. Compounds 2-5 were synthesized following the methods of reference 3. Compound 5 was oxidized following the method of reference 1. In this reaction, the purity of dimethyl pyrrole is important to decrease the amounts of the by-products. We used freshly distilled dimethyl pyrrole and kept it under inert gas atmosphere before use. Trifluoroacetic acid (TFA) catalyzes the reaction between aldehyde and dimethyl pyrrole. On the other hand, it increases the possibility of producing by-products by facilitating the polymerization of dimethyl pyrrole. We noticed that 10 µL of TFA per 1 g of dimethyl pyrrole is the optimum amount of TFA which can be used. Light shielding improves the yield of this reaction by decreasing the possibility of producing the polymerization product. Protecting the hydroxyl group of 1 helped us to produce alcohol 5 in high yield. We followed the method of reference 1 to oxidize alcohol 5 to aldehyde 6. The conditions of the reaction...
are milder than the one presented in reference 3 and the yield of the reaction is higher (88% compared to 68%).

2.2.2. Synthesis of compound 7

\[
\text{H} + \text{C} \xrightarrow{\text{HOAc, piperidine}} \text{NOAc, piperidine} \xrightarrow{\text{toluene, N}_2, \text{reflux}} \text{CN}
\]

In this reaction the amount of acetic acid is decisive for producing the by-product and consequently the yield of the reaction. The best results were achieved using 2 mmol piperidine and 3 mmol of acetic acid per 1 mmol of compound 6.

2.2.3. Synthesis of compound 8

\[
\text{O} \xrightarrow{1. \text{TFA}} \text{CO} \xrightarrow{2. \text{Et}N} \text{C} \xrightarrow{3. \text{BOP, DCM}} \text{CN, N}_2, \text{RT}
\]

Because of the use of acid chloride instead of aldehyde to produce the BODIPY, this method does not need the oxidation step. Similar to the case of using aldehyde, the amount of TFA must be controlled. The product can be purified by column chromatography (DCM/ Petroleum ether: 10-90%) or it can be crystallized from a mixture of acetone and water.

2.2.4. Synthesis of compound 9

\[
\text{POCl}_3, \text{EMF} \xrightarrow{\text{DCM, N}_2, \text{RT}} \text{N}
\]

Compound 9 was synthesized following the method of reference 4.

2.2.5. Synthesis of compound 10

\[
\text{O} \xrightarrow{1. \text{TFA}} \text{CN} \xrightarrow{2. \text{Et}N} \text{C} \xrightarrow{3. \text{BOP, DCM}} \text{CN, N}_2, \text{RT}
\]

Compound 10 was synthesized following the method of reference 17.

2.2.6. Synthesis of compound 15

We followed the method of reference 5 to synthesize compound 11. We improved the reduction step with respect to reference 6 to increase the yield of this step from 14% to 60%. We used tin chloride to reduce the nitro group to the amine group. It must be noticed that if the complexation step is done before the reduction process, the fluorides will be replaced with ethoxy groups during the reflux. Then we continued the procedures in reference 5 to synthesize compounds 13-15. Purification of the products in every step is helpful to increase the yield of the reaction by removing the competing by-products.
Experimental methods and characterizations

are milder than the one presented in reference 3 and the yield of the reaction is higher (88% compared to 68%).

2.2.2. Synthesis of compound 7

\[
\begin{array}{c}
\text{HOAc, piperidine} \\
\text{S, N, reflux}
\end{array}
\]

In this reaction the amount of acetic acid is decisive for producing the by-product and consequently the yield of the reaction. The best results were achieved using 2 mmol piperidine and 3 mmol of acetic acid per 1 mmol of compound 6.

2.2.3. Synthesis of compound 8

\[
\begin{array}{c}
\text{1. TFA} \\
\text{2. EN, } \text{N} \\
\text{3. DCM, HCl, RT}
\end{array}
\]

Because of the use of acid chloride instead of aldehyde to produce the BODIPY, this method does not need the oxidation step. Similar to the case of using aldehyde, the amount of TFA must be controlled. The product can be purified by column chromatography (DCM/ Petroleum ether: 10-90%) or it can be crystallized from a mixture of acetone and water.

Chapter 2

2.2.4. Synthesis of compound 9

\[
\begin{array}{c}
\text{POCl₃, EMF} \\
\text{DCM, HCl, RT}
\end{array}
\]

Compound 9 was synthesized following the method of reference 4.

2.2.5. Synthesis of compound 10

\[
\begin{array}{c}
\text{H}_2 \text{N} \\
\text{N}
\end{array}
\]

Compound 10 was synthesized following the method of reference 17.

2.2.6. Synthesis of compound 15

We followed the method of reference 5 to synthesize compound 11. We improved the reduction step with respect to reference 6 to increase the yield of this step from 14% to 60%. We used tin chloride to reduce the nitro group to the amine group. It must be noticed that if the complexation step is done before the reduction process, the fluorides will be replaced with ethoxy groups during the reflux. Then we continued the procedures in reference 5 to synthesize compounds 13-15. Purification of the products in every step is helpful to increase the yield of the reaction by removing the competing by-products.
Experimental methods and characterizations

2.2.6.1. Synthesis of compound 12

Compound 11 (0.33 g, 1.02 mmol) was dissolved in 20 ml of EtOH, SnCl$_2$ (0.95 g, 5 mmol) was added and the solution was refluxed for 8 h. Then the solution was poured into ice and was made basic by addition of 5% sodium bicarbonate (pH 7-8). The compound was extracted with ethyl acetate, the organic phase was washed with brine and dried over sodium sulphate. The solvent was evaporated and the residue purified by flash column chromatography (EtOAc/petroleum ether: 30-100%) to afford compound 12 (0.17 g, 60%).

The compound was extracted with ethyl acetate, the organic phase was washed with brine and dried over sodium sulphate. The solvent was evaporated and the residue purified by flash column chromatography (EtOAc/petroleum ether: 30-100%) to afford compound 12 (0.17 g, 60%).

2.2.7. Synthesis of compound 17

We synthesized compound 17 following the method of reference 3.

2.3. Synthesis of the catalysts

2.3.1. Synthesis of 2-dimethyl amino cyclohexyl amine

Compound 22 was synthesized following the literature method.

Compound 22 was synthesized following the literature method.
Experimental methods and characterizations

2.2.6.1. Synthesis of compound 12

Compound 11 (0.33 g, 1.02 mmol) was dissolved in 20 ml of EtOH, SnCl₂ (0.95 g, 5 mmol) was added and the solution was refluxed for 8 h. Then the solution was poured into ice and was made basic by addition of 5% sodium bicarbonate (pH 7-8). The compound was extracted with ethyl acetate, the organic phase was washed with brine and dried over sodium sulphate. The solvent was evaporated and the residue purified by flash column chromatography (EtOAc/petroleum ether: 30-100%) to afford compound 12 (0.17 g, 60%).

We synthesized compound 17 following the method of reference 3.

2.2.7. Synthesis of compound 17

We synthesized compound 17 following the method of reference 3.

2.3. Synthesis of the catalysts

2.3.1. Synthesis of 2-dimethyl amino cyclohexyl amine

Compound 22 was synthesized following the literature method.
2.3.2. Synthesis of catalyst 25

Compound 25 was synthesized following the literature method.

2.3.3. Synthesis of catalyst 26

In this reaction slow addition of thiophosgene and also the temperature are important factors to control the yield of the reaction.

2.3.4. Synthesis of catalysts 27

Catalyst 27 was synthesized by Hans Sanders following the literature method.

2.3.5. Synthesis of catalyst 28

Boc-L-Proline (0.5 g, 2.32 mmol) was dissolved in DMF (5 ml). HOBt (0.395 g, 2.55 mmol) and EDCI-HCl (0.39 g, 2.55 mmol) were added and the mixture was stirred at room temperature under nitrogen atmosphere for 0.5 h. Then ethyl 3,4-diaminobenzoate (0.458 g, 2.54 mmol) was added, followed by DiPEA (0.848 ml, 4.87 mmol). The mixture was stirred in this condition for 60 h. Water was added and the product extracted with EtOAc. The organic phase was separated, dried with sodium sulphate and the solvent was evaporated.

The product was purified by column chromatography on silica gel (EtOAc/Petroleum ether: 50-100% then MeOH/DCM: 10-50%). $[\alpha]_{D}^{22} = -18.4$. ¹H NMR (400 MHz, DMSO): $\delta$ (ppm) = 10.03 (br, 1H, NH), 8.65 (br, 1H, NH), 7.90 (d, 2H, J = 8 Hz, ArH), 7.56 (d, 1H, J = 8 Hz, ArH), 7.42 (br, 2H, NH₂), 6.76 (d, 1H, ArH), 4.54 (m, 1H, proline), 4.22 (q, 2H, CH₂), 3.26 (m, 2H, proline), 2.44 (m, 1H, proline), 2.06 (m, 1H, proline), 1.96 (m, 2H, proline), 1.27 (t, 3H, CH₃). ¹³C NMR (100 MHz, DMSO): 167.84, 165.88, 146.89, 128.60, 127.53, 121.29, 116.99, 115.06, 60.14, 59.66, 46.03, 30.05, 24.00, 14.72. IR: ν (cm⁻¹): 3419, 3336, 3219, 3131, 2979, 2906, 1679, 1633, 1599, 1249, 1194, 1020, 940. High resolution mass calculated for (C₁₄H₁₉N₃O₃): 277.14232, Found: 277.1433.

2.3.6. Synthesis of catalyst 29

Catalyst 29 was prepared following the procedure of reference 11.
Experimental methods and characterizations

2.3.2. Synthesis of catalyst 25

\[
\begin{align*}
\text{Compound 25 was synthesized following the literature method.}
\end{align*}
\]

2.3.3. Synthesis of catalyst 26

\[
\begin{align*}
\text{In this reaction slow addition of thiophosgene and also the temperature are important factors to control the yield of the reaction.}
\end{align*}
\]

2.3.4. Synthesis of catalysts 27

\[
\begin{align*}
\text{Catalyst 27 was synthesized by Hans Sanders following the literature method.}
\end{align*}
\]

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\text{Boc-L-Proline (0.5 g, 2.32 mmol) was dissolved in DMF (5 ml). HOBt (0.395 g, 2.55 mmol) and EDCI-HCl (0.39 g, 2.55 mmol) were added and the mixture was stirred at room temperature under nitrogen atmosphere for 0.5 h. Then ethyl 3,4-diaminobenzoate (0.458 g, 2.54 mmol) was added, followed by DIPEA (0.848 ml, 4.87 mmol). The mixture was stirred in this condition for 60 h. Water was added and the product extracted with EtOAc. The organic phase was separated, dried with sodium sulphate and the solvent was evaporated. The product was purified by column chromatography on silica gel (EtOAc/Petroleum ether: 50-100% then MeOH/DCM: 10-50%). } \\
\[\alpha\]_589^22 = -18.4, \text{ }^1H \text{ NMR (400 MHz, DMSO): } \delta \text{ (ppm) } = 10.03 \text{ (br, 1H, NH), 8.65 (br, 1H, NH), 7.90 (d, 2H, } \text{J = 8 Hz, ArH), 7.56 (d, 1H, J = 8 Hz, ArH), 7.42 (br, 2H, NH_{2}), 6.76 (d, 1H, ArH), 4.54 (m, 1H, proline), 4.22 (q, 2H, CH_{2}), 3.26 (m, 2H, proline), 2.44 (m, 1H, proline), 2.06 (m, 1H, proline), 1.96 (m, 2H, proline), 1.27 (t, 3H, CH_{3}). } \\
\text{ }^{13}C \text{ NMR (100 MHz, DMSO): 167.84, 165.88, 146.89, 128.60, 127.53, 121.29, 116.99, } \\
115.06, 60.14, 59.66, 46.03, 30.05, 24.00, 14.72. IR: \nu \text{ (cm}^{-1}) \text{: 3419, 3336, 3219, 3131, 2979, 2906, 2879, 1679, 1533, 1599, 1366, 1258, 1249, 1194, 1020, 940. High resolution mass calculated for (C_{14}H_{19}N_{3}O_{3}): 277.14232, Found: 277.1433.}
\end{align*}
\]

2.3.6. Synthesis of catalyst 29

\[
\begin{align*}
\text{Catalyst 29 was prepared following the procedure of reference 11.}
\end{align*}
\]
2.3.7. General procedure for immobilization of the catalysts on the surface of glass cover slips

2.3.7.1. Cover slips cleaning

Ten cover slips were washed in 3% Hellmanex III solution in water by sonication for 1 h at 40 °C. Then, the cover slips were sonicated in deionized water for 30 min and in EtOH for 1 h, respectively. Then, they were dried in the oven at 110 °C for 1 h. After cooling to room temperature, the cover slips were put in the ozone photoreactor for 2 h.

2.3.7.2. Cover slips modification

3 µl 3-(mercaptopropyl)trimethoxysilane was pipeted on both sides of every slide. Then, the slides were heated for 30 min under vacuum at 100 °C. After cooling under inert gas atmosphere, they were transferred to the coplin jar containing toluene and sonicated for 30 min. The silylated slides were rinsed with methanol and were stored in methanol at 4 °C prior to reaction with catalysts.

2.3.7.3. Catalysts immobilization

The holder containing ten slides was transferred to a flask equipped with a cooler, and 60 ml chloroform was added. After adding catalyst (3 mg) and AIBN (24 mg), the mixture was refluxed at 70 °C for 30 h under argon. Then, the slides were rinsed with chloroform and were left in the fume hood for 3 days to oxidize the unreacted thiols on the surface of the slides.

We measured the water contact angle after each step. After washing the cover slides the measured contact angle was 10°. After silanization the contact angle increased to 32°. The measured contact angle after connecting the catalyst to the surface of the glass was 57° for catalyst 30 and 52° for catalyst 31. The increasing contact angle is in agreement with the increased hydrophobicity of the surface that resulted from the successive changes of the functional groups.

2.3.8. Synthesis of catalyst 32

Catalyst 32 was synthesized by Hans Sanders. The key step shown here used the procedure of ref. 12.

2.4. Synthesis of the product BODIPYs

2.4.1. General procedure for the synthesis of compound 38

In a flask shielded from light, compound 15 (20 mg, 0.047 mmol) and catalyst (0.0047 mmol) were dissolved in 10 ml solvent. Then, benzylmercaptan (50 µL, 0.47 mmol) was added. The mixture was stirred at room temperature until the reaction was completed (TLC). The solvent was evaporated and the residue was purified by column chromatography (EtOAc/ Petroleum ether), (Chapter 3, Tables 1 and 2).

1H NMR (400 MHz, CDCl3): δ = 7.25 - 7.68 (m, 9H, ArH), 5.99 (s, 1H, pyrrole), 5.96 (s, 1H, pyrrole), 3.62 (s, 2H, CH2S), 3.42 - 3.52 (m, 2H, CH2), 2.93 - 3.02 (m, 1H, CH), 2.45 (s, 3H, CH3), 2.37 (s, 3H, CH3), 1.58 (s, 6H, CH3) ppm.

13C NMR (100 MHz, CDCl3): δ = 137.19, 130.14, 130.10, 129.24, 129.23, 128.31, 128.30, 128.20, 127.26, 127.25, 121.48, 43.12, 43.10, 37.61, 35.15, 34.14,
2.3.7. General procedure for immobilization of the catalysts on the surface of glass cover slips

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\[ \text{H NMR (400 MHz, CDCl}_3\]: } \delta = 7.25 - 7.68 (m, 9H, ArH), 5.99 (s, 1H, pyrrole), 5.96 (s, 1H, pyrrole), 3.62 (s, 2H, CH\text{2}S), 3.42 - 3.52 (m, 2H, CH\text{2}), 2.93 - 3.02 (m, 1H, CH), 2.45 (s, 3H, CH\text{3}), 2.37 (s, 3H, CH), 1.58 (s, 6H, CH\text{3}) ppm.

\[ \text{C NMR (100 MHz, CDCl}_3\]: } \delta = 137.19, 130.14, 130.10, 129.24, 129.23, 128.31, 128.20, 127.26, 127.25, 121.48, 43.12, 43.10, 37.61, 35.15, 34.14, \ldots \]
2.4.2. General procedure for the synthesis of compound 39

In a flask shielded from light, compound 17 (18.5 mg, 0.047 mmol) and catalyst (0.0047 mmol) were dissolved in 10 ml solvent. Then, benzylmercaptan (50 μL, 0.47 mmol) was added. The mixture was stirred at room temperature until the reaction was completed. The solvent was evaporated and the residue was purified by column chromatography (EtOAc/Petroleum ether), (Chapter 3, Table 5).

2.4.3. General procedure for the synthesis of compound 40

In a flask shielded from light, under nitrogen atmosphere, compound 15 (20 mg, 0.047 mmol) and catalyst (0.0047 mmol) were dissolved in 10 ml of solvent. Then, dimethyl malonate (54 μL, 0.47 mmol) was added. The resulting mixture was stirred at room temperature. After the reaction had completed, the solvent was evaporated and the residue was purified by column chromatography. (EtOAc/Petroleum ether), (Chapter 3, Table 5).

2.4.4. General procedure for the synthesis of compound 41

In a flask shielded from light, under nitrogen atmosphere, compound 17 (18.5 mg, 0.047 mmol) and catalyst (0.0047 mmol) were dissolved in 10 ml of solvent. Then, dimethyl malonate (54 μL, 0.47 mmol) was added. The resulting mixture was stirred at room temperature. After completing the reaction, the solvent was evaporated and the residue was purified by column chromatography. (EtOAc/Petroleum ether), (Chapter 3, Table 6).
2.4.2. General procedure for the synthesis of compound 39

In a flask shielded from light, compound 17 (18.5 mg, 0.047 mmol) and catalyst (0.0047 mmol) were dissolved in 10 ml of solvent. Then, benzyl mercaptan (50 μL, 0.47 mmol) was added. The mixture was stirred at room temperature until the reaction was completed. The solvent was evaporated and the residue was purified by column chromatography (EtOAc/Petroleum ether), (Chapter 3, Table 5).

2.4.3. General procedure for the synthesis of compound 40

In a flask shielded from light, under nitrogen atmosphere, compound 15 (20 mg, 0.047 mmol) and catalyst (0.0047 mmol) were dissolved in 10 ml of solvent. Then, dimethyl malonate (54 μL, 0.47 mmol) was added. The resulting mixture was stirred at room temperature. After the reaction had completed, the solvent was evaporated and the residue was purified by column chromatography. (EtOAc/Petroleum ether), (Chapter 3, Table 5).
2.4.6. General procedure for the synthesis of compound 43

To a solution of compound 18 (0.03 mmol) in 4 ml of the solvent, dimedone (4.2 mg, 0.03 mmol) and catalyst (0.002 mmol) were added and the solution was stirred at room temperature. After consumption of starting materials, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/Petroleum ether), to obtain the product. 1H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) (ppm) = 7.49 (m, 3H, ArH), 7.33 (m, 2H, ArH), 7.21 (t, 2H, J = 8 Hz, ArH), 5.28 (s, 2H, CH\textsubscript{2}), 2.56 (s, 2H, CH\textsubscript{2}), 2.56 (s, 2H, CH\textsubscript{2}), 2.48 (AB pattern, 2H, \( \Delta \delta = 0.09 \) ppm, \( J = 20 \) Hz, CH\textsubscript{2}), 2.31 (AB pattern, 2H, \( \Delta \delta = 0.16 \) ppm, \( J = 16 \) Hz, CH\textsubscript{2}), 1.35 (s, 6H, CH\textsubscript{3}), 1.11 (s, 3H, CH\textsubscript{3}), 0.98 (s, 3H, CH\textsubscript{3}).

IR: \( \nu \) (cm\textsuperscript{-1}) = 3450, 3338, 3220, 2954, 2192, 1676, 1597, 1541, 1507, 1467, 1360, 1295, 1273, 1257, 1138, 1038, 971. High resolution mass calculated for \((C\textsubscript{13}H\textsubscript{14}BF\textsubscript{2}O\textsubscript{5}N\textsubscript{2}+\text{Na})\): 527.2039, Found: 527.2029.

2.4.7. General procedure for the synthesis of compound 44

After consumption of starting materials, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/Petroleum ether), to obtain the product. 1H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) (ppm) = 7.50 (m, 3H, ArH), 7.43 (d, 2H, J = 8 Hz, ArH), 5.98 (s, 1H, CH\textsubscript{3}), 1.11 (s, 3H, CH\textsubscript{3}), 0.98 (s, 3H, CH\textsubscript{3}).

IR: \( \nu \) (cm\textsuperscript{-1}) = 3450, 3338, 3220, 2954, 2192, 1680, 1664, 1598, 1537, 1512, 1465, 1358, 1309, 1191, 1158, 976. Mass calculated for \((C\textsubscript{13}H\textsubscript{14}BF\textsubscript{2}O\textsubscript{5}N\textsubscript{2}+\text{Na})\): 527.2039, Found: 527.2029.

2.4.8. General procedure for the synthesis of compound 45

After consumption of starting materials, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/Petroleum ether), to obtain the product. 1H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) (ppm) = 5.60 (s, 6H, CH\textsubscript{3}), 1.85 (s, 3H, CH\textsubscript{3}), 1.85 (s, 3H, CH\textsubscript{3}), 1.11 (s, 3H, CH\textsubscript{3}), 0.98 (s, 3H, CH\textsubscript{3}).

IR: \( \nu \) (cm\textsuperscript{-1}) = 3450, 3338, 3220, 2954, 2192, 1676, 1597, 1541, 1507, 1467, 1360, 1295, 1273, 1257, 1138, 1038, 971 cm\textsuperscript{-1}. High resolution mass calculated for \((C\textsubscript{13}H\textsubscript{14}BF\textsubscript{2}O\textsubscript{5}N\textsubscript{2}+\text{Na})\): 527.2039, Found: 527.2029.
2.4.5. General procedure for the synthesis of compound 42

To a solution of compound 7 (8 mg, 0.02 mmol) in 4 ml of the solvent, dinedone (4.2 mg, 0.03 mmol) and catalyst (0.002 mmol) were added and the solution was stirred at room temperature. After consumption of starting materials, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/Petroleum ether), to obtain the product. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.43 (d, 2H, $J = 8$ Hz, ArH), 7.23 (d, 2H, $J = 8$ Hz, ArH), 5.98 (s, 2H, CH-pyrorrole), 4.61 (s, 2H, CH$_2$), 4.52 (s, 1H, CH$_2$), 2.56 (s, 6H, CH$_3$), 2.48 (AB pattern, 2H, $\Delta\delta$ = 0.09 ppm, $J = 20$ Hz, CH$_2$). $\Delta\delta$ = 0.16 ppm, $J = 16$ Hz, CH$_3$), 1.35 (s, 6H, CH$_3$), 1.14 (s, 3H, CH$_3$), 0.98 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$): 195.24, 161.11, 157.46, 154.18, 144.04, 143.09, 133.59, 128.52, 127.87, 121.02, 117.99, 113.85, 99.81, 62.89, 50.45, 40.48, 35.35, 31.92, 28.97, 26.72, 14.39, 14.09. IR: v (cm$^{-1}$): 3450, 3338, 3220, 2954, 2192, 1676, 1597, 1541, 1507, 1467, 1360, 1305, 1213, 1190, 1038, 971. High resolution mass calculated for (C$_{38}$H$_{2}$BF$_{2}$N$_{2}$O$_{2}$): 540.25081, Found: 540.24910.

2.4.6. General procedure for the synthesis of compound 43

To a solution of compound 10 (8 mg, 0.02 mmol) in 4 ml of the solvent, dinedone (4.2 mg, 0.03 mmol) and catalyst (0.002 mmol) were added and the solution was stirred at room temperature.

After consumption of starting materials, the reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/Petroleum ether), to obtain the product. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) = 7.49 (m, 3H, ArH), 7.33 (m, 2H, ArH), 5.98 (s, 1H, CH-pyrorrole), 4.51 (s, 2H, NH$_2$), 4.43 (s, 1H, CH$_2$), 2.56 (s, 6H, CH$_3$), 2.40 (AB pattern, 2H, $\Delta\delta$ = 0.06 ppm, $J = 16$ Hz, CH$_3$), 2.23 (AB pattern, 2H, $\Delta\delta$ = 0.03 ppm, $J = 16$ Hz, CH$_3$), 1.58 (s, 6H, CH$_3$), 1.11 (s, 3H, CH$_3$), 1.08 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$): 195.75, 161.08, 157.14, 155.14, 143.04, 135.07, 131.48, 129.89, 128.94, 128.08, 121.09, 118.23, 112.19, 61.20, 50.54, 47.04, 40.41, 31.99, 28.40, 28.00, 25.61, 14.47, 12.48, 11.39, 8.62. IR: v (cm$^{-1}$): 3388, 3175, 2957, 1933, 1680, 1654, 1598, 1537, 1512, 1465, 1358, 1309, 1159, 1158, 976. Mass calculated for (C$_{38}$H$_{2}$BF$_{2}$N$_{2}$O$_{2}$)+CH$_{3}$CN+Na: 604.26713, Found: 604.26829 and Mass calculated for (C$_{38}$H$_{2}$BF$_{2}$N$_{2}$O$_{2}$)+Na: 563.2406, Found: 563.2344.
acetoacetate (30 μL, 0.23 mmol) were added. The reaction was stirred at room temperature. After evaporation of the solvent the product was purified using column chromatography (ethyl acetate/ petroleum ether: 15% to 100%), then ethyl acetate/methanol: 9/1). 1H NMR (400 MHz, CDCl3): δ (ppm) = 7.48 (d, 2H, J = 8 Hz, ArH), 7.26 (d, 2H, J = 8 Hz, ArH), 7.99 (s, 2H, CH-pyrrrole), 5.64 (s, 1H, NH), 5.49 (s, 1H, NH), 4.06 (m, 2H, CH2), 2.57 (s, 6H, CH3), 2.43 (s, 3H, CH3), 1.34 (s, 6H, CH3), 1.15 (t, 3H, CH3). 13C NMR (100 MHz, CDCl3): 165.19, 155.51, 152.27, 146.16, 144.74, 142.78, 140.92, 134.72, 131.21, 128.34, 127.48, 121.17, 100.93, 59.93, 55.85, 18.65, 14.47, 14.25, 14.07. IR: ν (cm−1): 3225, 2977, 2929, 1697, 1648, 1545, 1510, 1306, 1228, 1195, 1089, 982. High resolution mass calculated for (C29H38F2N2O): 506.23008, Found: 506.23010.

References:

(9) Kotke, M.; Schreiner, P. R. Acid-Free, Organocatalytic Acetalization.
acetoacetate (30 μL, 0.23 mmol) were added. The reaction was stirred at room temperature. After evaporation of the solvent the product was purified using column chromatography (ethyl acetate/petroleum ether: 15% to 100%), then ethyl acetate/methanol: 9/1). $^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) = 7.48 (d, 2H, J = 8 Hz, ArH), 7.26 (d, 2H, J = 8 Hz, ArH), 5.99 (s, 2H, CH-pyrrrole), 5.64 (s, 1H, NH), 5.49 (s, 1H, NH), 4.06 (m, 2H, CH$_2$), 2.57 (s, 6H, CH$_3$), 2.43 (s, 3H, CH$_3$), 1.34 (s, 6H, CH$_3$), 1.15 (t, 3H, CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$): 165.19, 155.51, 152.27, 146.16, 144.74, 142.78, 140.92, 134.72, 131.21, 128.34, 127.48, 121.17, 100.93, 59.93, 55.85, 18.65, 14.47, 14.25, 14.07. IR: ν (cm$^{-1}$): 3225, 2977, 2929, 1697, 1648, 1545, 1510, 1306, 1228, 1195, 1089, 982. High resolution mass calculated for (C$_{21}$H$_{12}$FeN$_2$O$_4$): 506.23008, Found: 506.23010.

References:


(9) Kotke, M.; Schreiner, P. R. Acid-Free, Organocatalytic Acetalization.
Chapter 3

Fluorescence turn-on in organocatalytic Michael reactions

3.1. Introduction
The Michael reaction is the addition of nucleophiles such as carbon, sulfur, nitrogen and oxygen anions to the β position of an α,β-unsaturated carbonyl compound or an alkene with a cyano, nitro or sulfonyl substituent. It has been widely used as one of the steps to introduce new functional groups into molecules for the construction of complex structures. Carbon nucleophiles are mostly alkyl metal halides found in organometallic reagents, enolates and also enols. Oxygen nucleophiles are water, hydroxide, alkoxide and carboxylate anions. Hydrogen sulfide and its salts, thiols, thiolates, thiocarboxylic anions are the mostly used sulfur nucleophiles. Examples of nitrogen nucleophiles are ammonia, azide, amines and nitrites. Due to the advantages of organocatalytic synthesis considerable attention has been paid to this method in organic chemistry. For instance, progress in organocatalytic asymmetric Michael reactions has led to new compounds which are the building blocks of natural products and drugs. Despite the considerable progress in the synthesis of new compounds, selecting the catalyst and the condition of the reaction are still challenging. Having knowledge about the interaction between catalyst and substrates will help to better understand the mechanism of the reactions and consequently improve the selection or design of the catalyst for a particular reaction. Different methods such as NMR, ESI-MS, and quantum mechanical calculations have been used to figure out the mechanism of organocatalytic reactions. Still there is room to study this area more deeply. In this chapter we explore fluorescence spectroscopy as a tool to follow the interaction between substrate and catalyst and to monitor product formation in the organocatalytic Michael addition of benzyl mercaptan and dimethyl malonate to non-fluorescent compounds 15 and 17 to produce the strongly fluorescent products 36 – 41 (Schemes 4, 7-9).