Chemistry and characterization of the graphene basal plane and edge for recognition tunneling

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Chapter 3

Investigation of the reactivity of mercapto-aniline precursors on the C-H arylation using pyrene as a model substrate for graphene via diazonium chemistry

Abstract

Thiolation of graphene, by covalent attachment through mercapto-(aryl) diazonium salts, has the major drawback of forming disulfide bonds during the diazotization. The formed disulfide may thereafter impede the functionalization on graphene. Here, disulfide formation is suppressed during the diazotization by protecting the thiol with a benzoyl group. Using pyrene as a model system for graphene allowed investigating for, both, alkane and phenolic thiols, with - and without a benzoyl group, the difference in reactivity on the covalent functionalization of graphene through diazonium chemistry. Without a benzoyl group the hydrogen atom transfer side reaction hampers the double C-H arylation reaction. Incorporation of a benzoyl protecting group suppressed the formation of disulfides and led to the isolation of a single pyrene-arylated product in 21% yield for the alkanethiol and 22% for the thiophenol precursor over two steps. Introducing a nitro group ameliorated the yield of the latter to 46%. Furthermore, the benzoyl group is stable under electrochemical conditions used for covalent functionalization of graphene. On a broader perspective, the combination of distinct side chain functional groups with aryl diazonium salts (or other functionalization strategies) will suffer from various side reactions and pre-emptive capping (that is, protecting) the functional group with a benzoyl group may mitigate these side reactions, thus ameliorating the covalent functionalization on graphene.

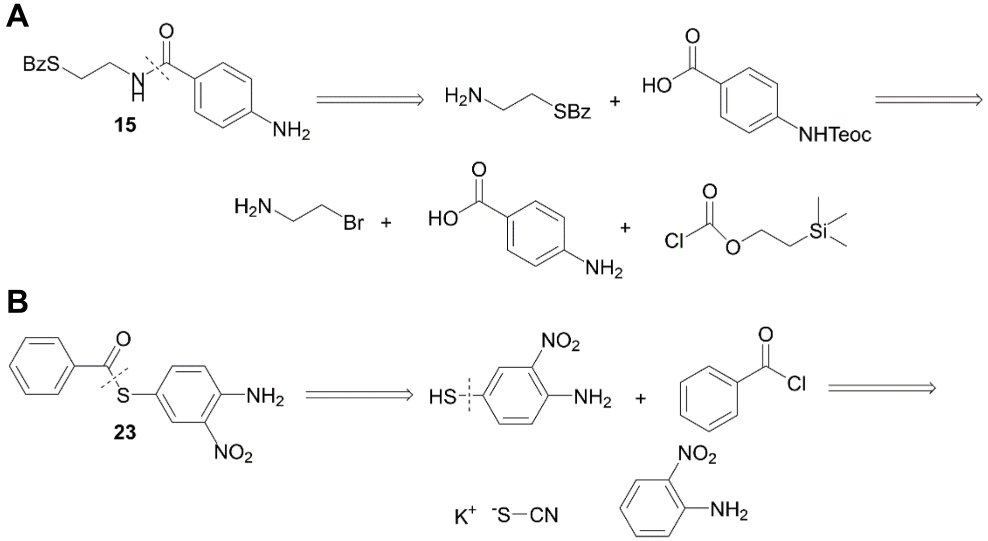
3.1 Introduction

Thiolation of graphene by covalently functionalizing graphene with alkane/phenolic thiols via diazonium chemistry,[1-3] predominantly to anchor gold nanoparticles (AuNPs), suffers from the formation of disulfides during the diazotization. The formed disulfide facilitates side-reactions during the subsequent radical reaction and thereby hampers the formation of a carbon-carbon bond with graphene. Protecting the alkane – and phenolic thiol with a benzoyl (Bz) group suppressed the formation of disulfides. Furthermore, taking pyrene as a model substrate to resemble graphene, made it possible to elaborate on the difference in chemical reactivity (that is, between the protected and unprotected alkane – and phenolic thiol diazonium salts) on the C-H arylation of pyrene. While oligomerization[4, 5] and the influence of the substrate on graphene reactivity[6-8] have gained attention, the intermolecular compatibility of side chain functional groups is often overlooked. Therefore, the study also discusses how the obtained results can affect the thiolation of graphene, through diazonium chemistry, to emphasize the role of side-chain functionalities in chemistry on graphene. Lastly, electrochemical reduction of aryl diazonium salts is a common strategy to achieve covalent functionalization of graphene. As such, the stability of the incorporated Bz-group toward electrochemical reduction of aryl diazonium salts was studied by subjecting the alkanethiol containing aniline precursor to cyclic voltammetry (CV) measurements.

Other approaches to immobilize AuNPs include non-covalent functionalization,[9, 10] and direct deposition via drop casting,[11] electrodeposition,[11, 12] *in situ* reduction of a gold salt[13-15] or evaporation[16, 17]. Unsurprisingly, as immobilization via non-covalent approaches rely on weaker interactions[18] the immobilized particles are susceptible to desorption. Through the direct deposition approaches it is difficult to control the density, size and/or morphology of the particles,[15, 19] parameters that can be of importance for certain applications, such as surface-enhanced Raman spectroscopy.[20, 21] Immobilization of AuNPs on graphene, through the formation of Au-S bonds, introduced by coupling a mercapto molecule on graphene, results in a robust bond and enables the use of specific sized AuNPs. Radical chemistry is an appealing approach to achieve covalent functionalization of graphene.[22] Particularly diazonium chemistry has obtained interest for its relatively straightforward synthesis and high reactivity.[23, 24] Immobilization of AuNPs through a thiol on small organic molecules, covalently bound to graphene via radical chemistry, has been achieved via two approaches: decorating the AuNPs with the thiolated molecules and thereafter covalently functionalizing graphene[25] or thiolation of graphene followed by immersion of the functionalized graphene in a suspension of AuNPs.[26-28] In the case of diazonium chemistry, the formed radical can react with gold[27, 29, 30] upon homolytic cleavage of the diazonium group.[31] Also from a stability perspective of the (aryl) diazonium salt the latter approach is more convenient.

A noteworthy result within the attempts to immobilize AuNPs after thiolation of graphene (in this particular case obtained by covalently functionalizing graphene with alkanethiols via diazonium chemistry) is that the formation of Au-S bonds only occurred by immersing the thiolated graphene during the *in situ* synthesis of AuNPs.[32] The result seems in contrast with preceding cited literature that anchored AuNPs on distinct solid-materials through incubation in already grown AuNP suspensions. A possible explanation for the seeming discrepancy is that thiolation of the distinct solid-materials proceeded with thiophenol-based aryl diazonium salts instead of alkanethiol-based diazonium salts.

The different results in immobilizing AuNPs described in the previous paragraphs (that is, the ability to immobilize already grown particles) implies that diazotization leads to the pre-dominant formation of disulfides in the case of alkanethiols and that the thiophenol derivatives may be less prone toward the formation of disulfides. Furthermore, formation of disulfides may affect the covalent binding of such small organic molecules on graphene. Therefore, suppressing the formation of disulfides, by the introduction of a Bz-group, could possibly ameliorate the coupling onto graphene. Obtaining quantitative data on graphene functionalization is difficult,[22] but taking pyrene as a model system for graphene enables the use of common analysis techniques utilized within synthetic organic chemistry. Thus, the compatibility of alkane and phenolic thiols toward diazotization and the consequences of the formed disulfide on the subsequent radical reaction could be investigated. Suppressing disulfide formation was achieved by introducing a Bz-group on mercapto-aniline precursors (**Scheme 3.1**).



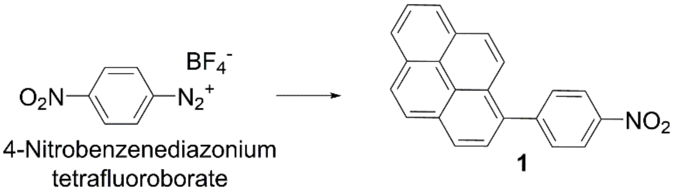
Scheme 3.1. Retrosynthesis of two Bz-protected mercapto-aniline precursors. Route **A**) Coupling of protected 4-aminobenzoic acid with Bz-protected cysteamine. Route **B**) Introduction of thiocyanate and hydrolysis to obtain thiolated 2-nitroaniline. Incubation with benzoyl chloride then yielded a Bz-protected thiol.

Route **A** illustrates the design of precursor **15**. Forming an amide bond between a Bz-protected cysteamine and an aminobenzoic acid derivative yielded the mercapto-group. The Bz-protected cysteamine intermediate resulted from a three-step modification starting with 2-bromoethylamine. For the aminothiophenol derivative (compound **23**) adding a nitro-group served to enhance the reactivity compared to Bz-protected 4-aminothiophenol (not shown here). Route **B** shows the retrosynthesis for compound **23**. Synthesis proceeded by capping 2-nitro-4-thioaniline with a Bz-group. 2-Nitro-4-thioaniline resulted from 2-nitroaniline in a two-steps procedure via the introduction of a thiocyanate followed by hydrolysis with potassium hydroxide (KOH).

3.2 Results & Discussion

The literature reports different catalysts to facilitate displacement of the diazonium group and/or to aid the C-H arylation (that is, the radical reaction).[33, 34] Thus, to probe the effectiveness of different catalysts on the chemical reaction, pyrene and 4-nitrobenzenediazonium tetrafluoroborate (4-NBD) were mixed with different catalysts (**Scheme 3.2**). The option for 4-

NBD derives from its stability, commercial availability and strong reactivity due to the electron withdrawing properties of the nitro-group.[35, 36] The tested reaction conditions and obtained results are shown below (**Table 3.1**).

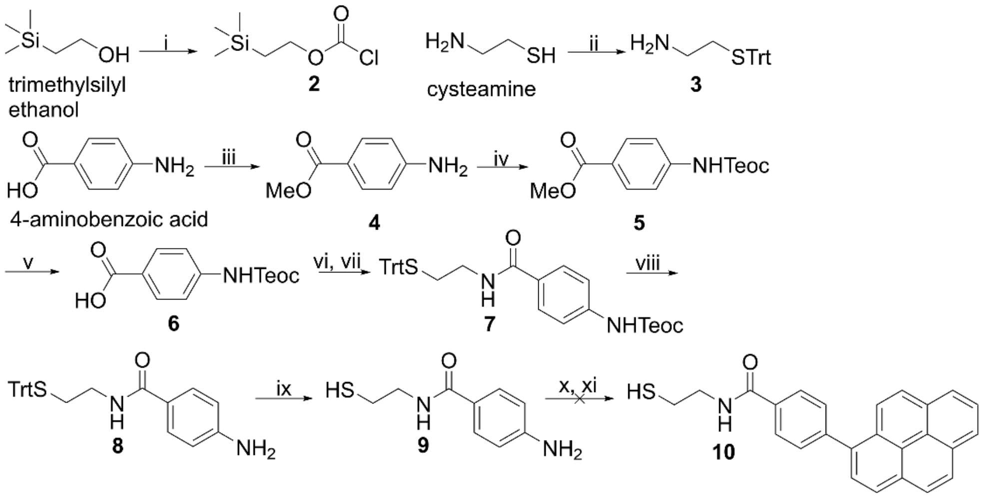


Scheme 3.2. Reaction scheme of the C-H arylation test reaction. 4-NBD as substrate and pyrene as model compound to resemble graphene.

Table 3.1. Summary of the different tested conditions to facilitate the C-H arylation. All reactions were carried out in DCM – acetone (1:1) at a 0.50 mmol scale.

Catalyst	**Time (days)**	**Yield (%)**
Light	7	21
Ascorbic acid	2	40
Ferrocene	2	52

Mixing pyrene and 4-NBD in 1:1 dichloromethane (DCM) - acetone followed by stirring for extended time (seven days), with daylight as catalyst, resulted in arylated pyrene **1** with 21% yield. Adding a reducing agent such as ascorbic acid increased the yield to 40% after two days and replacing ascorbic acid by ferrocene ameliorated the yield to 52%. It is worth stating that slight deviations of the yield can occur as the hydrophobic nature of compound **1** may result in co-elution of the product with unreacted pyrene during the purification step. The yield of the reaction catalyzed by ferrocene is similar to the reported value of the arylation of pyrene with benzenediazonium tetrafluoroborate. As the procedure has been applied on various compounds with moderate to good yield, ferrocene was adopted as catalyst to assess the reactivity of the mercapto-aniline precursors toward diazotisation and C-H arylation. The synthesis of the first target compound concerned unprotected alkanethiol aniline **9** (**Scheme 3.3**).



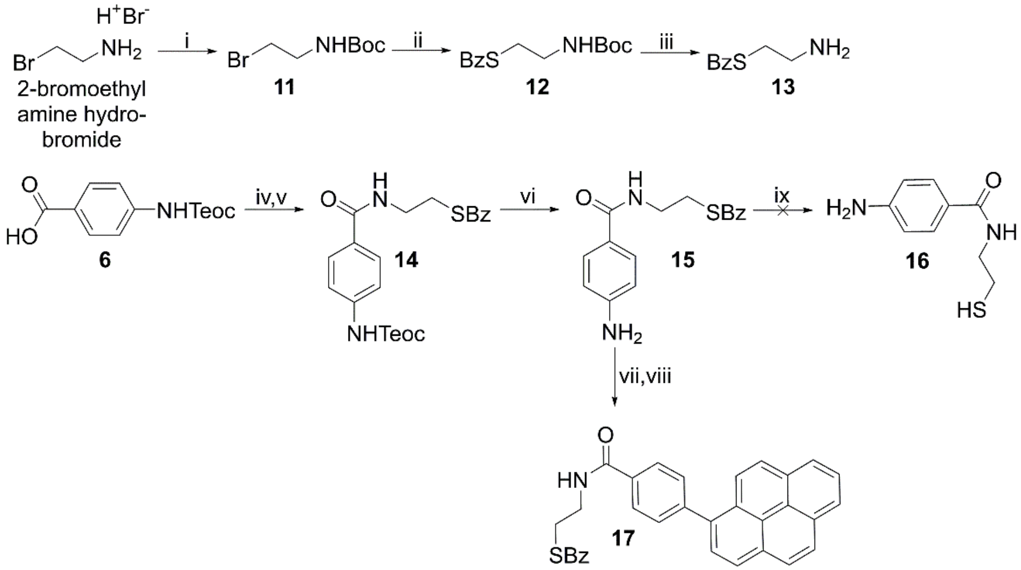
Scheme 3.3. Synthetic route for an exposed mercapto-aryl diazonium salt. *Reaction conditions*: (i) Phosgene (20% wt. in toluene), K_2CO_3, toluene, -10 °C to rt, 2.5 h, 78%. (ii) Trt-Cl, TFA, rt, 4 h, 92%. (iii) H_2SO_4, MeOH, 100 °C, 20 h, quantitative. (iv) **2**, pyridine, DCM, 0 °C to rt, o/n, 73%. (v) LiOH (aq.), dioxane, rt, o/n, 98%. (vi) $SOCl_2$, DCM - DMF, 55 °C, 2 h. (vii) **3**, NEt_3, DCM, 0 °C to rt, o/n, 60% (over 2 steps). (viii) TBAF (1.0 M), DMF, o/n, rt, 60%. (ix) DCM - TFA - H_2O - TES (6.1:3.1:0.40:0.40), rt, 1.5 h, 88%. (x) $NOBF_4$, DCM - acetone, -10 °C, 2 h. (xi) Ferrocene, pyrene, acetone, rt, 2 days.

The synthesis started by stirring trimethylsilylethanol in a solution of phosgene in toluene (20%) for two and a half hours to obtain 2-(trimethylsilyl)ethyl chloroformate (Teoc-Cl) **2** in 78% yield. The Teoc-protecting group bears orthogonality toward mild acidic and alkaline conditions.[37] Treatment of cysteamine with trityl-chloride (Trt-Cl) in trifluoroacetic acid (TFA) for four hours provided trityl-protected cysteamine **3** in 92% yield. Overnight methylation of 4-aminobenzoic acid in methanol (MeOH) and sulfuric acid (H_2SO_4) afforded methyl ester **4** in quantitative yield. Teoc-protected methyl ester **5** was obtained in 73% yield by reaction of **4** with **2** using pyridine as acid scavenger. Saponification with lithium hydroxide (LiOH) converted the ester to carboxylic acid **6** in 98% yield. Converting acid **6** to the acyl chloride proceeded through the Vilsmeier reagent involving an excess thionyl chloride ($SOCl_2$) with a catalytic amount of dimethylformamide (DMF).[38] The overnight treatment of the crude acyl chloride with cysteamine **3** afforded protected building block **7** in 60% yield over two steps. Addition of tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF) provided a source of fluorides ions to cleave the Teoc-group; Attack of the fluoride ion on the silicon atom followed by β-elimination furnished deprotected amine **8** in 60% yield. Lastly, treatment of amine **8** with trifluoroacetic acid (TFA) and triethylsilane (TES) as scavenger offered target compound **9** in 15% yield over nine steps. Diazotization by slow addition of nitrosonium tetrafluoroborate ($NOBF_4$) at -10 °C into a mixture of DCM-acetone (1:1) containing compound **9** would convert the amine into the corresponding diazonium salt. After two hours of stirring, the obtained dark solution was evaporated to yield a sticky oil. Directly subjecting the sticky oil to the C-H arylation using the ferrocene procedure showed, via analysis by liquid chromatography - mass spectrometry (LC-MS) (**Fig. S3.1**), the formation of predominantly three difficult to separate species, one indicative of the expected product (compound **10**). The two other observed masses align with disulfide by-products, one where the amide bond is cleaved (**Fig. S3.2A**) referred to as compound **A** and the other that suggests the hydrogen atom transfer side-reaction (**Fig. S3.2B**) referred to as compound **B**.

Attempts to quantify the data to receive an estimate of the obtained ratios between the different products turned difficult as varying the gradient in the chromatographic separation turned unsuccessful. The presence of compound **B** is noteworthy as it suggests that after the primary C-H arylation hydrogen atom transfer occurs, preventing a second C-H arylation and thereby the formation of the double pyrene arylated species. Particularly for graphene, additional factors influence the functionalization density as coupling the mercapto-aryl molecule at both sides on graphene would confine the molecule in a configuration that may not be favorable due to steric factors and bond angles that do not affect the hydrogen atom transfer side reaction. Furthermore, theoretical calculations showed that after the primary attached aryl group, the second most reactive carbon atom on graphene is the *para*-position indicating that the initial reaction influences (albeit generally increases) the reactivity of the surrounding carbon atoms.[39] However, the reaction may be dominated by kinetics instead of thermodynamics owing to the radical approach.[40] Other factors that influence the final reactivity include the chemical strategy to achieve covalent functionalization and the imperfect state (e.g., impurities, doping, defects) of the graphene lattice in practice. While the external perturbations existing on graphene make it difficult to predict if the aryl coupling will prevail over hydrogen atom transfer, the inability to detect a double pyrene bearing species implies that hydrogen atom transfer is intrinsically favored over the second C-H arylation, thereby reducing the amount of mercapto-aryl molecules coupled with pyrene. Thus, the formed disulfides may also affect the number of molecules that will bind on graphene.

The observation of disulfide formation also explains the reported inability to detect a chemical bond between the alkanethiol functionalized graphene and the AuNPs upon immersing the thiolated graphene with pre-grown AuNP suspensions.[32] For graphene covalently functionalized with thiophenol moieties via diazonium chemistry that did achieve AuNP decoration by incubation with pre-grown AuNP suspensions, it may be that the thiophenol variants are less prone toward formation of disulfides under the diazotization conditions. This notion is supported by the observation that during electrochemical chemisorption of mercapto-aryl diazonium salts, the electrochemical cleavage of disulfides proceeds at potentials far beyond the potential window used for covalent functionalization of graphene. Therefore cleavage of disulfides during the functionalization step can be excluded.[41, 42] As reduction of the disulfide during electrochemical chemisorption can be excluded it is also unlikely that disulfides are being cleaved during most chemical strategies implemented to covalently functionalize graphene. Thus, the observed differences in AuNP attachment lies in the intrinsic tendency of the precursors to form disulfides.

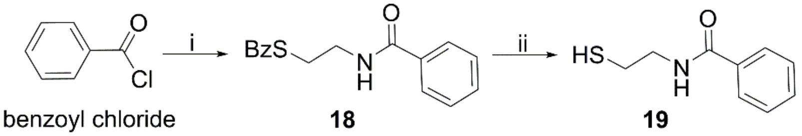
Based on the inability to purify/analyze the obtained mixture an alternative approach, to investigate whether the formation of disulfides impede the covalent functionalization, was made by executing the C-H arylation with protected thiols. With the Trt-group (that is, compound **8**) getting cleaved during the diazotization, the Bz-group, hydrolyzed under alkaline conditions, was instead evaluated as suitable protection agent (**Scheme 3.4**).



Scheme 3.4. Synthetic route for a Bz-protected mercapto-aryl aniline precursor. *Reagent and conditions*: (i) Boc_2O, NEt_3, DCM, 0 °C to rt, o/n, quantitative. (ii) Thiobenzoic acid, Cs_2CO_3, DMF, rt, o/n, 89%. (iii) TFA – DCM (1:1), rt, 1.5 h, 82%. (iv) $SOCl_2$, DCM – DMF, 55 ºC, 2 h. (v) **13**, DIPEA, DCM, 0 °C to rt, o/n, 61% (over 2 steps). (vi) TBAF (THF, 1.0 M), ACN, o/n, rt, 33%. (vii): $NOBF_4$, DCM - acetone, -10 °C, 2 h. (viii) Ferrocene, pyrene, acetone, rt, 2 days, 26% (over 2 steps). (ix) NaOMe, MeOH, rt, 5 h.

Tert-butoxycarbonyl (Boc)-protection of 2-bromoethylamine with di-*tert*-butyl dicarbonate (Boc_2O) and triethylamine (NEt_3) as base furnished compound **11** in quantitative yield. Subsequent thiolation with thiobenzoic acid and cesium carbonate (Cs_2CO_3) in DMF provided thiol linker **12** in 89 % yield. Selective deprotection of the Boc-group by stirring thiol linker **12** in a mixture of TFA – DCM (1:1) at room temperature provided amine **13** in 82% yield. Thiol linker **13** coupled to acid **6** as previously described gave linker **14** in 61% yield. Removal of the Teoc-group with TBAF resulted in target compound **15** in 33% yield. Diazotization of amine **15** with $NOBF_4$ yielded an easy to filtrate solid that could subsequently be dissolved into acetone – DCM (1:1) to conduct the ferrocene mediated C-H arylation. A single product isolated over two steps in 21% yield turned to be pyrene arylated compound **17**. Albeit low, in contrast to the same reaction with compound **9**, the outcome of the procedure showed that the benzoyl group is suitable to protect the thiol during C-H arylation of polyaromatics via diazonium chemistry.

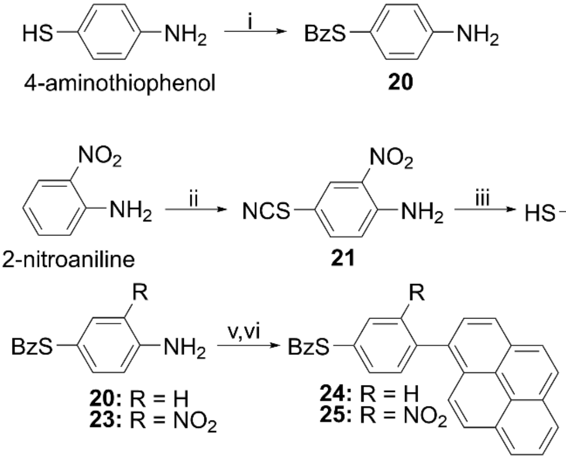
Next step in the successful C-H arylation (by obtaining compound **17**) entailed the hydrolysis of the newly formed thioester to recover the thiol. Suspending compound **15** in dry MeOH followed by addition of a freshly prepared solution of sodium methoxide (NaOMe) in dry MeOH (0.20 M) created an alkaline medium to facilitate the hydrolysis. However, instead of thioester hydrolysis (compound **16**), NMR revealed cleavage of the amide. The hypothesis is that the electron donating effect of the amine favors hydrolysis of the amide over the ester. Synthesis of a similar linker in absence of the amine and subjecting the synthesized linker molecule to the same hydrolysis conditions validated this hypothesis (**Scheme 3.5**).



Scheme 3.5. Hydrolysis of a Bz-protected thiol linker in absence of the amine. *Reagents and conditions*: (i) **13**, DIPEA, DCM, rt, o/n, 83%. (ii) NaOMe, MeOH, rt, 2 h, 60%.

Mixing benzoyl-chloride with compound **13** in presence of Hünig's base afforded compound **18** overnight. Thereafter, subjecting **19** to the aforementioned hydrolysis conditions led to cleavage of the thioester to give the thiol. Unlike the amine variant, the isolation of compound **19** as white crystals in 60% yield indicated that the amine disrupted hydrolysis of the thioester. As covalent functionalization of compound **15** on graphene results in a C-C bond with conversion of a sp^2 hybridized carbon atom to a sp^3 hybridized carbon atom on graphene[43] any delocalization effects as a result of the π-π network of graphene should not be able to affect the hydrolysis.

Most preceding strategies to covalently functionalize solid-materials, based on diazonium chemistry with thiols, have been performed with 4-aminothiophenol.[26-28] Performing the diazotization and C-H arylation with mercapto-aryl diazonium salt precursors on pyrene gave an indication on how the diazotization and C-H arylation proceeds on a thiophenol derivative (**Scheme 3.6**). Not surprisingly (data not shown), the diazotization and subsequent C-H arylation of pyrene with 4-aminothiophenol also resulted in the formation of disulfide by-products (**Fig. S3.2C** and **D**). Identical to the Bz-protected alkane aryl diazonium salt, performing the diazotization and C-H arylation with the benzoylated variant (compound **20**) allowed facile isolation of a single product (compound **24**).



Scheme 3.6. Schematic overview of the synthesized phenolic thiol precursors and subsequent diazotization and C-H arylation with pyrene. *Reagents and conditions:* (i) Benzoyl-chloride, NEt_3, DCM, 4 h, rt, 20%. (ii) Bromine, NaSCN, AcOH, 1.5 h, 0-5 °C, 59%. (iii) KOH, EtOH, 3 h, 0-5 °C, 53%. (iv) Benzoyl chloride, NEt_3, DCM, o/n, rt, 50%. (v) $NOBF_4$, DCM - acetone, -10 °C/0-5 °C, 2 h. (vi) Ferrocene, pyrene, DCM – acetone (1:1), rt, 2 days, **24** 22%, **25** 46% (over 2 steps).

Direct addition of benzoyl chloride to a mixture of 4-aminothiophenol with NEt_3 at 0 °C furnished target compound **20**. Performing the diazotization and C-H arylation yielded arylated pyrene **24** in 22% over two steps. An attempt to further improve the yield came by synthetizing the same compound carrying an *o*-nitro group. Mixing 2-nitroaniline with liquid bromine (Br_2), acetic acid and sodium thiocyanate resulted in a subsequent electrophilic bromination, followed by a nucleophilic aromatic substitution of the thiocyanate anion to give thiocyanate **21** in 59% yield after one and a half hours. Subsequent hydrolysis with KOH in ethanol (EtOH) furnished thiol **22** in 57% after three hours that, after protection with benzoyl chloride and NEt_3 ended in target compound **23** in 50% yield. Performing the diazotization and C-H arylation yielded product **25** in 46% yield instead of 22%, hence improving the overall reaction efficiency.

Naturally, utilizing a protected thiol requires an additional step (that is, removal of the benzoyl) and therefore mandates to investigate the efficiency of the deprotection, on e.g., graphene, to properly address if applying this protecting group will result in, for example, higher density of AuNPs. However, it is believed that, other than the difficulties observed in handling the diazotized form of the unprotected thiol variants, paying more attention on the side chain functional groups present in the precursors will benefit the density of the diazotized molecules covalently functionalized on solid-materials. Particularly as, for in this case with thiols, a direct reaction between alkane thiols with aryl diazonium salts has been reported.[44]

The intrinsic properties of graphene make that it is highly explored as electrode material. Unsurprisingly, electrochemical reduction of aryl diazonium salts became a common strategy to achieve covalent functionalization of graphene. Especially as electrochemical functionalization of graphene proceeds rapidly as opposed to chemical reduction. Furthermore, electrochemical reduction the diazonium salt is achieved by modulating the Fermi level of graphene. This significantly increases its reactivity and therefore presumably yields a higher functionalization density than chemically functionalizing graphene.[24] Therefore, the stability of the Bz-group toward electrochemical conditions (at a potential range used to reduce aryl diazonium salts)[45] was investigated. The experimental setup consisted of a three-electrode setup with a platinum work electrode, gold counter electrode, Ag/AgCl pseudo-reference electrode and a solution with 18 mg of precursor **15**. A cyclic voltammetry (CV) measurement of 100 cycles performed between -0.40 V and +0.20 V at a scan rate of 50 mV s^{-1} (**Fig. S3.3**) revealed, after extraction of the compound from the solution and analysis by NMR, that the benzoyl remained intact (**Fig. S3.4** and **S3.5**) under electrochemical conditions relevant for reduction of aryl diazonium salts and therefore for conditions relevant for covalent functionalization of graphene. Based on the NMR, obtained with the recovered 14 mg (78%) out of the added 18 mg it is concluded that the Bz-group is a viable protecting group for thiolation of graphene under electrochemical conditions.

3.3 Conclusion

Diazotization of, both, alkane - and phenolic thiols resulted in the formation of disulfides. Diazotization and C-H arylation of the alkane thiol (that is, compound **9**) with pyrene yielded a complex mixture comprising two side-products, other than the desired product, resembling amide cleavage and hydrogen atom transfer side reaction. The hydrogen transfer side reaction also occurs with the thiophenol derivative. Protection with a Bz-group supressed disulfide formation and allowed facile isolation of a single product, suggesting that the hydrogen atom transfer side reaction (and potentially other unidentified side-reactions), after disulfide formation, competes with or occurs instead of coupling to a second pyrene molecule, thereby impeding the C-H arylation. Although difficult to conclude, it is expected, due to additional steric constraints, that these side-reactions are also prevalent upon reacting with graphene and thereby impede the functionalization density. Lastly, upon exposing the Bz-protected molecule **15** to electrochemical conditions it was possible to recover 78% of the compound showing that the benzoyl group is stable under electrochemical conditions relevant for covalent functionalization for graphene. On a broader perspective, it is recommended to consider the influence of side-chain functional group(s) present in the precursor prior to the diazotization and covalent functionalization of solid-materials, to obtain higher functionalization densities and/or a stronger intendent effect of the attached molecule.

3.4 Supporting information

3.4.1 Electrochemistry

Cleaning of glassware and electrodes was achieved with ultrapure water (>18.2 MΩ cm resistivity). Electrochemical experiments were performed using a three-electrode setup in a single-compartment, custom-made glass cell. Sodium sulfate (Na_2SO_4, Suprapur®, Merck) (0.1 M dissolved in ultrapure water was used as electrolyte. The measured compound was dissolved in 1.5% v/v of acetonitrile prior to adding to the cell. Experiments were conducted on a PGSTAT204 using the NOVA 2.1 software. All other chemicals were purchased from Sigma Aldrich, Acros, VWR, Merck and Fischer Scientific and used as obtained.

Before each experiment all the required glassware was cleansed by overnight immersion in a potassium permanganate (aq.) ($KMnO_4$) (1 g/L) solution in sulfuric acid (H_2SO_4) (0.5 M). This was followed by rinsing with ultrapure water (5x). Re-oxidation of any non-oxidized traces of MnO_2 and cleaning was achieved by immersing the glassware in a highly diluted piranha solution. Lastly, all the glassware was rinsed (5x), boiled (3x) and rinsed again (5x) with ultrapure water to remove traces of impurity.

Argon (Linde, Ar 5.0) was purged through each electrolyte solution for 30 minutes prior to the experiment and during the experiment the cell was kept under a constant argon flow. In all experiments, the reference electrode (RE) was an Ag/AgCl reference electrode (<3.0 kΩ, Metrohm) in a glass shaft filled with an aq. KCl (3.0 M) and sat. AgCl solution. The counter electrode (CE) was a gold nanorod connected with copper wires. A platinum sheet electrode (1 cm^2, Metrohm) was used as work electrode (WE).

3.4.2 Synthesis

Materials and Methods

Chemicals were purchased from Sigma Aldrich, Acros, VWR, Merck and Fischer Scientific and used as obtained. Anhydrous solvents were prepared by drying over activated molecular sieves (3Å/4Å respectively) for at least 24 hours prior to use. Activation of molecular sieves was achieved by flame-drying under reduced pressure. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. Unless stated all reactions were performed at room temperature. Commercially available ACS grade solvents were used without further purification. Reactions and chromatography fractions were monitored by thin layer chromatography (TLC). TLC analysis was conducted using Merck aluminium sheets (Silica gel 60 F254) with detection by UV absorption (254 nm), by spraying with a solution of $KMnO_4$ (20 g/L) and K_2CO_3 (10 g/L) in water. Column chromatography was performed using Screening Devices b.v. silica gel 60 (particle size of 40 – 63 µm, pore diameter of 60 Å) with the indicated eluent. TLC-MS analysis was conducted by taking spots off a TLC plate with a CAMAG TLC interface connected to an API 165 mass spectrometer. ^1H and ^{13}C-APT NMR spectra were recorded on a Brüker AV-300 (300 and 75 MHz respectively), AV-400 (400 and 101 MHz respectively), Brüker DMX-500 (500 and 126 MHz respectively) or a Brüker DMX-850 (850 and 213 MHz respectively) in the given solvent. Chemical shifts (δ) are given in parts per million (ppm) relative to the residual solvent peak. Coupling constants are given in Hz. Liquid chromatography-mass spectrometry (LC-MS) analysis was performed on a Finnigan LCQ Advantage MAX using a C18-column. The sample had a final concentration of 20 µM. A 10-90 MeCN + 0.1% trifluoroacetic acid (TFA) gradient was used over 12.5 minutes. High-resolution mass spectrometry (HRMS) spectra were obtained from a Thermo Finnigan LTQ orbitrap mass spectrometer.

General diazotization procedure

The amine (0.20 mmol, 1.0 eq.) was suspended in 1:1 DCM - acetone (0.1 M) under a nitrogen atmosphere. The suspension was cooled to 0 ºC or -10 ºC and $NOBF_4$ (1.1 – 2.0 eq.) was added in portions. The resulting suspension was stirred for 1-2.5 hours and decanted in cold Et_2O. The precipitate was filtrated and washed with cold Et_2O (3x). The remaining solid was left to dry under a nitrogen atmosphere.

General procedures for C-H arylation of pyrene

For the commercially available 4-NBD the aryl diazonium salt (0.50 mmol) was used as reference. For all C-H arylations a mixture of the 1,1’ and 2,1’ products is suspected to have been isolated as depicted in literature.[46] The annotation of the NMR spectrum has only been performed for the major product (that is, the 1,1’ product).

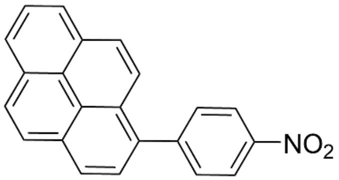
Procedure A. Pulverized pyrene (3.0 eq.) was added to a mixture of 1:1 DCM – acetone (0.1 M) under a nitrogen atmosphere and left to stir for ~ five minutes. Thereafter, the mixture was cooled to 0 °C and the aryl diazonium salt was added in portion. This was left to stir for seven days at room temperature and evaporated. Finally, the arylated product was purified by silica column chromatography.

Procedure B. Pulverized pyrene (3.0 eq.) was added to a mixture of 1:1 DCM – acetone (0.1 M) under a nitrogen atmosphere and left to stir for ~ five minutes. Thereafter, the mixture was cooled to 0 °C and the aryl diazonium salt was added in portion followed by a freshly prepared solution of L-ascorbic acid (0.10 eq.) in DMSO (0.5 M). This was left to stir for two days at room temperature, diluted with DCM and washed with sat. $NaHCO_3$ (aq.), water and brine. The organic layer was dried over $MgSO_4$ and evaporated. Finally, the arylated product was purified by silica column chromatography.

Procedure C. Pulverized pyrene (3.0 eq.) was added to a mixture of 1:1 DCM – acetone (0.17 M) under a nitrogen atmosphere and left to stir for ~ five minutes. Thereafter, the mixture was cooled to 0 °C and the aryl diazonium salt was added in portion followed by slow addition of ferrocene (0.10 eq.) in acetone (0.17 M). This was left to stir for two days at room temperature, diluted with DCM and washed with sat. $NaHCO_3$ (aq.), water and brine. The organic layer was dried over $MgSO_4$ and evaporated. Finally, the arylated product was purified by silica column chromatography.

3.4.3 Supporting experimental section

1-(4-nitrophenyl)pyrene (1)



C-H arylation was performed with all three described procedures. Purification by silica column chromatography was performed in toluene – pentane (3:7) to yield a mixture with compound **1** as major product as an orange powder (85 mg, 0.26 mmol, 52%) R_f = 0.33 (3:7 Toluene – Pentane). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 8.44 – 8.40 (m, 2H, CH_{phenyl}), 8.27 – 8.23 (m, 3H, CH_{pyrene}), 8.21 (d, J = 7.8 Hz, 1H, CH_{pyrene}), 8.15 – 8.00 (m, 4H, CH_{pyrene}), 7.94 (d, J = 7.9 Hz, 1H, CH_{pyrene}), 7.79 (dt, J = 8.8, 2.0, Hz, 2H, CH_{phenyl}). **^{13}C-APT NMR** ($CDCl_3$, 101 MHz): δ 148.17 ($C_{q,phenyl}$), 147.12 ($C_{q,phenyl}$), 134.90 ($C_{q,pyrene}$), 131.48 ($C_{q,pyrene}$), 131.43 (CH_{phenyl}), 130.81 ($C_{q,pyrene}$), 130.31 ($C_{q,pyrene}$), 128.41 (CH_{pyrene}), 128.31 ($C_{q,pyrene}$), 128.23 (CH_{pyrene}), 127.32 (CH_{pyrene}), 127.20 (CH_{pyrene}), 126.38 (CH_{pyrene}), 125.76 (CH_{pyrene}), 125.38 (CH_{pyrene}), 124.95 ($C_{q,pyrene}$), 124.77 (CH_{pyrene}), 124.72 ($C_{q,pyrene}$), 124.20 (CH_{pyrene}), 123.70 (CH_{phenyl}). Spectral data were in accordance with those reported in literature.[46]

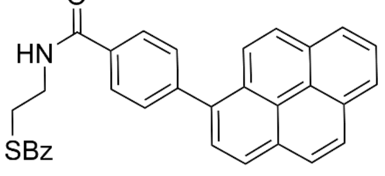
Procedure A. Compound **1** (34 mg, 0.11 mmol, 21%).

Procedure B. Compound **1** (65 mg, 0.20 mmol, 40%). The reaction mixture was diluted in DCM (20 mL) and washed with sat. $NaHCO_3$ (aq.) (3x 20 mL), water (5x 20 mL) and brine (3x 20 mL).

Procedure C. Compound **1** (85 mg, 0.26 mmol, 52%).

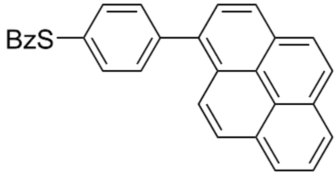
The reaction mixture was diluted in DCM (20 mL) and washed with sat. $NaHCO_3$ (aq.) (3x 20 mL), water (3x 20 mL) and brine (3x 20 mL).

2-(*S*)-(*N*-(4-(pyrene-1-yl)benzamido)ethyl)thiobenzoate (17)



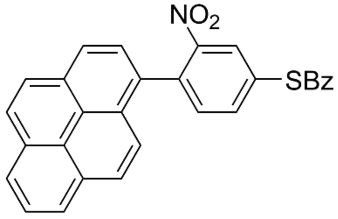
Diazotization was achieved with compound **16** (60 mg, 0.20 mmol, 1.0 eq.) and $NOBF_4$ (26 mg, 0.22 mmol, 1.1 eq.) by stirring at -10 °C for 1.5 hours. C-H arylation was achieved with procedure **C**: The reaction mixture was diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (aq.) (3x 10 mL), water (3x 10 mL) and brine (3x 10 mL). Purification by silica column chromatography (4:6 EtOAc – Pentane) provided compound **17** as major product (mixture) as a vanilla coloured powder (25 mg, 52 µmol, 26%) over two steps. R_f = 0.62 (4:6 EtOAc – Pentane). **^{1}H-NMR** ($CDCl_3$, 850 MHz): δ 8.23 (t, J = 7.6 Hz, 2H, CH_{pyrene}), 8.19 – 8.16 (m, 3H, CH_{pyrene}, CH_{phenyl}), 8.14 – 8.09 (m, 3H, CH_{pyrene}), 8.06 – 8.01 (m, 1H, CH_{pyrene}), 7.95 (d, J = 7.6 Hz, 1H, CH_{pyrene}), 7.83 (dd, J = 8.2, 1.5 Hz, 2H, CH_{bz}), 7.73 (d, J = 7.7 Hz, 2H, CH_{phenyl}), 7.51 (t, J = 7.8 Hz, 1H, CH_{bz}), 7.45 (t, J = 7.4 Hz, 2H, CH_{bz}), 6.83 (t, J = 5.5 Hz, 1H, NH), 3.84 (q, J = 5.9 Hz, 2H, CH_2), 3.44 (t, J = 6.3 Hz, 2H, CH_2). **^{13}C-APT NMR** ($CDCl_3$, 213 MHz): δ 192.63 (CO_{bz}), 167.76 ($CO_{cysteamine}$), 147.16 ($C_{q,phenyl}$), 136.12 ($C_{q,phenyl}$/$C_{q,bz}$), 135.55 ($C_{q,pyrene}$), 134.33 ($C_{q,phenyl}$/$C_{q,bz}$), 131.69 (CH_{bz}), 131.56 ($C_{q,pyrene}$), 131.27 ($C_{q,pyrene}$), 131.08 (CH_{phenyl}), 131.00 ($C_{q,pyrene}$), 128.73 (CH_{bz}), 128.45 ($C_{q,pyrene}$), 128.16 (CH_{pyrene}), 128.05 (CH_{pyrene}), 127.60 (CH_{phenyl}), 127.47 (CH_{pyrene}), 127.37 (CH_{pyrene}), 127.12 (CH_{bz}), 126.35 (CH_{pyrene}), 125.63 (CH_{pyrene}), 125.29 (CH_{pyrene}), 125.07 ($C_{q,pyrene}$), 124.91 ($C_{q,pyrene}$), 124.84 (CH_{pyrene}), 124.73 (CH_{pyrene}), 40.70 (NCH_2), 28.78 (SCH_2). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_{32}H_{32}NO_2SH]^+$: 486.14, found 486.15.

4-(*S*)-((pyrene-1-yl)phenyl)thiobenzoate (24)



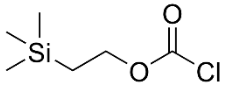
Diazotization was achieved with compound **20** (46 mg, 0.20 mmol, 1.0 eq.) and $NOBF_4$ (26 mg, 0.22 mmol, 1.1 eq.) by stirring at 0 °C for 1.5 hours. C-H arylation was achieved with procedure **C**: The reaction mixture was diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (aq.) (3x 10 mL), water (3x 10 mL) and brine (3x 10 mL). Purification by silica column chromatography (3:7 Toluene – Pentane) provided compound **24** (18 mg, 44 µmol, 22%) as major product (mixture) as a light brown powder over two steps. R_f = 0.3 (3:7 Toluene – Pentane). **^{1}H-NMR** ($CDCl_3$, 850 MHz): δ 8.26 – 8.21 (m, 3H, CH_{pyrene}), 8.20 – 8.18 (m, 1H, CH_{pyrene}), 8.13 – 8.11 (m, 4H, CH_{Bz}, CH_{pyrene}), 8.09 – 8.01 (m, 3H, CH_{pyrene}), 7.75 (d, J = 8.2 Hz, 2H, CH_{phenyl}), 7.73 (d, J = 8.2 Hz, 2H, CH_{phenyl}), 7.65 (t, J = 7.5 Hz, 1H, CH_{bz}), 7.54 (t, J = 7.8 Hz, 2H, CH_{Bz}). **^{13}C-APT NMR** ($CDCl_3$, 213 MHz): δ 190.44 (CO), 142.68 ($C_{q,phenyl}$), 136.80 ($C_{q,phenyl}$/$C_{q,bz}$), 136.72 ($C_{q,phenyl}$/$C_{q,Bz}$), 135.13 (CH_{phenyl}), 133.91 (CH_{bz}), 131.60 ($C_{q,pyrene}$), 131.58 (CH_{phenyl}), 131.09 ($C_{q,pyrene}$), 131.01 ($C_{q,pyrene}$), 128.96 ($CH_{2,bz}$), 128.59 ($C_{q,pyrene}$), 127.89 (CH_{pyrene}), 127.80 (CH_{pyrene}), 127.70 ($CH_{2,bz}$), 127.65 (CH_{pyrene}), 127.53 (CH_{pyrene}), 126.45 ($C_{q,pyrene}$), 126.23 (CH_{pyrene}), 125.40 (CH_{pyrene}), 125.18 (CH_{pyrene}), 125.13 (CH_{pyrene}), 125.09 ($C_{q,pyrene}$), 124.99 ($C_{q,pyrene}$), 124.84 (CH_{pyrene}). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_{29}H_{18}OSH]^+$: 415.11, found 415.11.

4-(*S*)-(2-nitro(pyrene-1-yl)phenyl)thiobenzoate (25)



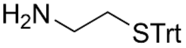
Diazotization was achieved with compound **23** (55 mg, 0.20 mmol, 1.0 eq.) and $NOBF_4$ (46 mg, 0.40 mmol, 2.0 eq.) by stirring at 0 °C for 2.5 hours. C-H arylation was achieved with procedure **C**: The reaction mixture was diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (aq.) (3x 10 mL), water (3x 10 mL) and brine (3x 10 mL). Purification by silica column chromatography (3:7 Toluene – Pentane) provided compound **25** (42 mg, 92 µmol, 46%) as major product (mixture) as a dark orange powder over two steps. R_f = 0.44 (1:1 Toluene – Pentane). **^{1}H-NMR** ($CDCl_3$, 850 MHz): δ 8.33 (d, J = 1.9 Hz, 1H, CH_{phenyl}), 8.25 – 8.22 (m, 2H, CH_{pyrene}), 8.20 – 8.18 (d, J = 7.4 Hz, 1H, CH_{pyrene}), 8.14 – 8.10 (m, 2H, CH_{pyrene}), 8.09 (d, J = 8.3 Hz, 2H. CH_{bz}), 8.06 – 8.00 (m, 2H, CH_{bz}), 7.91 (d, J = 7.7 Hz, 1H, CH_{pyrene}), 7.89 (dd, J = 7.7, 1.9 Hz, 1H, CH_{phenyl}), 7.78 (d, J = 8.9 Hz, 1H, CH_{pyrene}), 7.68 (t, J = 7.5 Hz, 2H, CH_{phenyl}, CH_{bz}), 7.55 (t, J = 7.7 Hz, 2H, CH_{bz}). **^{13}C-APT NMR** ($CDCl_3$, 213 MHz): δ 188.65 (CO), 150.12 ($C_{q,phenyl}$), 138.81 (CH_{phenyl}), 136.84 ($C_{q,phenyl}$), 136.00 ($C_{q,bz}$), 134.36 (CH_{phenyl}), 134.21(CH_{bz}), 131.73 ($C_{q,phenyl}$), 131.48 ($C_{q,pyrene}$), 131.38 ($C_{q,pyrene}$), 130.86 ($C_{q,pyrene}$), 130.55 (CH_{phenyl}), 129.11 ($C_{q,pyrene}$), 129.06 (CH_{bz}), 128.67 ($C_{q,pyrene}$), 128.53 (CH_{pyrene}), 128.10 (CH_{pyrene}), 127.71 (CH_{bz}), 127.36 (CH_{pyrene}), 126.29 (CH_{pyrene}), 126.25 (CH_{pyrene}), 125.72 (CH_{pyrene}), 125.49 (CH_{pyrene}), 124.75 ($C_{q,pyrene}$), 124.70 (CH_{pyrene}), 124.68 ($C_{q,pyrene}$), 123.92 (CH_{pyrene}). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_{29}H_{17}OSH]^+$: 460.10, found 460.10.

(2-(trimethylsilyl)ethoxy)carbonyl chloride (2)



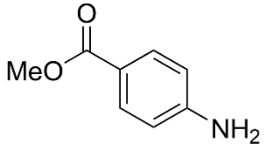
Trimethylsilylethanol (4.4 mL, 30 mmol, 1.0 eq.) and potassium carbonate (K_2CO_3) (3.6 g, 26 mmol, 0.90 eq.) were suspended in anh. toluene (17 mL, 1.7 M) in a 100 mL flask under a nitrogen atmosphere. The resulting mixture was cooled to -10 °C. Phosgene (20% in toluene, 21 mL, 39 mmol, 1.3 eq.) was slowly added dropwise and the resulting mixture was stirred for 30 mins at -10 °C before allowed to warm up to room temperature. After stirring for 2.5 hours the excess of phosgene was removed by passing a stream of nitrogen gas through the flask for two hours. The remaining solution was washed with sat. sodium carbonate (aq.) (Na_2CO_3) (3x 20 mL). The solution was evaporated (water bath temperature max. 30 °C, pressure max 50 mbar) to remove any leftover phosgene and the remaining residue was dissolved in Et_2O (50 mL) and dried over $MgSO_4$. A stream of nitrogen was passed through the flask to remove the solvent and obtain compound **2** (4.1 g, 23 mmol, 76%) as a colorless oily liquid that was used without further purification. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 4.41 (t, J = 8.9 Hz, 2H, OCH_2), 1.13 (t, J = 8.9 Hz, 2H, $SiCH_2$), 0.06 (s, 9H, CH_3). **^{13}C-APT NMR** ($CDCl_3$, 101 MHz): δ 150.61 (CO), 71.43 (OCH_2), 17.59 ($SiCH_2$), -1.49 (CH_3).

(*S*)-tritylcysteamine (3)



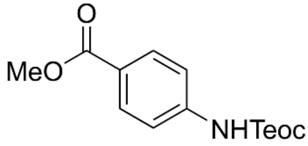
To a 500 mL flask trityl-chloride (29 g, 0.10 mol, 1.0 eq.) and cysteamine (8.1 g, 0.10 mol, 1.0 eq.) were added under a nitrogen atmosphere. TFA (0.11 L, 0.9 M) was added and the resulting red dense liquid was stirred for four hours. Afterwards TFA was evaporated and NaOH (aq.) (0.40 L, 2.0 M) was added. This was left to incubate overnight. The resulting white precipitate was filtrated and washed with water (3x 0.20 L) and pentane (3x 0.20 L). Purification by silica column chromatography (1:9 MeOH – DCM) provided compound **3** (40 g, 92 mmol, 92%) as a cream colored solid. R_f = 0.59 (1:9 MeOH – DCM). **^{1}H-NMR** ($(CD_3)_2SO$, 500 MHz): δ 7.38 – 7.32 (m, 12H, H_{trityl}), 7.28 – 7.23 (t, J = 6.9 Hz, 3H, H_{trityl}), 2.58 (t, J = 8.7 Hz, 2H, $NCH_{cysteamine}$), 2.48 (t, J = 8.7 Hz, 2H, $SCH_{cysteamine}$). **^{13}C-APT NMR** ($(CD_3)_2SO$, 126 MHz): δ 144.13 ($C_{q,trityl}$), 129.10 (CH_{trityl}), 128.21(CH_{trityl}), 126.95 (CH_{trityl}), 66.41 ($C_{q,trityl}$), 37.97 (NCH_2), 29.09 (SCH_2). Spectral data were in accordance with those reported in literature.[47]

methyl 4-aminobenzoate (4)



4-Aminobenzoic acid (4.1 g, 30 mmol, 1.0 eq.) and methanol (43 mL, 0.7 M) were added to a 100 mL flask. Sulfuric acid (95-97%) (3.0 mL) was added dropwise and the resulting suspension was refluxed at 100 °C for 20 hours. The mixture was evaporated and water (50 mL) was added to the residue. Saturated sodium carbonate (aq.) was added until pH ≈ four. Dichloromethane (30 mL) was added and the resulting emulsion was transferred into a separation funnel. The organic layer was separated and the aqueous layer was extracted with DCM (3x 30 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated. This provided compound **4** (4.5 g, 30 mmol, 100%) as a white solid. R_f = 0.71 (1:1 EtOAc – Pentane). **^{1}H-NMR** (MeOD, 300 MHz): δ 7.72 (d, J = 8.9 Hz, 2H, CH_{phenyl}), 6.62 (d, J = 8.9 Hz, 2H, CH_{phenyl}), 3.80 (s, 3H, CH_3). **^{13}C-APT NMR** (CD_3OD, 75 MHz): δ 169.29 ($C_{q,ester}$), 154.70 ($C_{q,phenyl}$), 132.47 (CH_{phenyl}), 118.52 ($C_{q,phenyl}$), 113.81 (CH_{phenyl}), 51.95 (CH_3). Spectral data were in accordance with those reported in literature.[48]

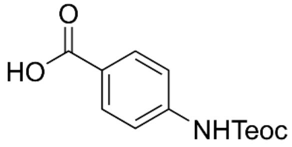
methyl 4-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)benzoate (5)



A dropping funnel was connected to a two-neck 500 mL flask. Under a nitrogen atmosphere compound **4** (2.3 g, 15 mmol, 1.0 eq.) and DCM (0.14 L, 84 mM) were added. The solution was cooled to 0 °C and pyridine (3.1 mL, 38 mmol, 2.5 eq.) was added dropwise. The solution was allowed to stir for five minutes before compound **2** (5.4 g, 30 mmol, 2.0 eq.) dissolved in DCM (40 mL) was poured into the dropping funnel and dropwise added to the reaction mixture. The resulting mixture was allowed to warm to room temperature and left to stir overnight. After completion water (0.10 L) was added and the organic layer was separated. The aqueous layer was extracted with DCM (3x 50 mL) and the combined organic layers were washed with brine (3x 50 mL), dried over $MgSO_4$ and evaporated. Purification by silica column chromatography (3:7 Et_2O – Pentane) provided compound **5** as a yellow solid (3.3 g, 11 mmol, 73%). R_f = 0.71 (3:7 Et_2O – Pentane). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ 7.99 (d, J = 8.9 Hz, 2H, CH_{phenyl}), 7.45 (d, J = 8.9 Hz, 2H, CH_{phenyl}), 6.78 (s, 1H, NH), 4.27

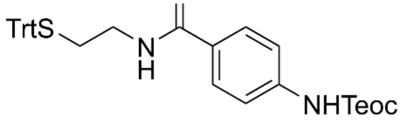
(d, J = 8.7 Hz, 2H, OCH_2), 3.89 (s, 3H, $CH_{3,ester}$), 1.05 (d, J = 8.7 Hz, 2H, $SiCH_2$), 0.06 (s, 9H, $CH_{3,silyl}$). **^{13}C-APT NMR** ($CDCl_3$, 101 MHz): δ 166.82 ($C_{q,ester}$), 153.39 ($C_{q,phenyl}$), 142.47 (CO_{teoc}), 131.07 (C_{phenyl}), 124.81 ($C_{q,phenyl}$), 117.62 (C_{phenyl}), 64.13 ($OCH_{2,Teoc}$), 52.11 ($CH_{3,methyl}$), 17.87 ($SiCH_{2,teoc}$), -1.35 ($CH_{3,silyl}$). Spectral data were in accordance with those reported in literature.[49]

4-(*N*-((2-(trimethylsilyl)ethoxy)carbonyl)amino)benzoic acid (6)



Compound **5** (3.2 g, 11 mmol, 1.0 eq.) was added to a 250 mL round-bottom flask and dioxane (82 mL, 0.13 M). Lithium hydroxide monohydrate ($LiOH·H_2O$) (0.72 g, 17 mmol, 1.6 eq., 0.5 M aq. solution) was added dropwise and the resulting solution was stirred overnight. The reaction was quenched by dropwise addition of five% AcOH until the mixture reached pH ≈ 4. The mixture was added in a separatory funnel and EtOAc (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification by silica column chromatography (3:7 Et_2O – Pentane + 1% AcOH) afforded compound **6** as a white solid (2.9 g, 9.3 mmol, 87%). R_f = 0. (3:7 Et_2O – Pentane + 1% AcOH). **^{1}H-NMR** ($(CD_3)_2CO$, 500 MHz): δ 8.95 (s, 1H, NH), 7.98 (d, J = 8.8 Hz, 2H, CH_{phenyl}), 7.69 (d, J = 8.8 Hz, 2H, CH_{phenyl}), 4.26 (t, J = 8.5 Hz, 2H, OCH_2), 1.06 (t, J = 8.5 Hz, 2H, $SiCH_2$), 0.07 (s, 9H, CH_3). **^{13}C-APT NMR** ($(CD_3)_2CO$, 126 MHz): δ 167.21 ($C_{q,carboxylic\ acid}$), 154.32 ($C_{q,phenyl}$), 144.63 (CO_{teoc}), 131.56 (C_{phenyl}), 125.09 ($C_{q,phenyl}$), 118.18 (C_{phenyl}), 63.65 ($OCH_{2,teoc}$), 18.21 ($SiCH_{2,teoc}$), -1.49 ($CH_{3,silyl}$). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_{13}H_{19}NO_4SiH]^+$: 282.11, found 282.11.

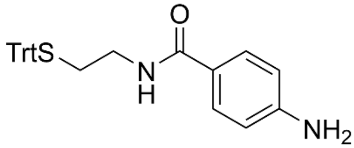
2-((*S*)-trityl)ethyl-(*N*)-4-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)benzamido (7)



Compound **6** (5.6 g, 20 mmol, 1.0 eq.) was dissolved in anh. DCM (1.0 L, 20 mM). Thionyl chloride ($SOCl_2$) (24 mL, 0.36 mol, 17 eq.) and DMF (77 µL, 5.0 mol%) were added and the resulting mixture was refluxed at 55 °C for two hours.

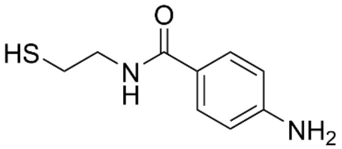
Completion of the reaction was confirmed by transferring a small sample into a LC-MS vial and adding acetonitrile and *n*-butylamine. The obtained mixture was then analyzed by LC-MS for the amide derivative. Once conversion to the acid chloride was confirmed the solution was cooled to room temperature and evaporated. Excess of $SOCl_2$ was removed by co-evaporation with toluene (3x). Separately compound **3** (11g, 25 mmol, 1.3 eq.) was suspended in anh. DCM (0.16 L, 0.16 M) under a nitrogen atmosphere. Then NEt_3 (8.0 mL, 50 mmol, 2.5 eq.) was added and after everything dissolved the resulting solution was cooled to 0 °C. The obtained acid chloride was added portion wise as a solid and the resulting solution was left to stir overnight. The organic layer was washed with sat. $NaHCO_3$ (aq.) (3x 0.10 L), water (3x 0.10 L) and brine (3x 0.10 L). Purification by silica column chromatography afforded yielded compound **7** as a white solid (11 g, 19 mmol, 95%). R_f = 0.67 (3:7 EtOAc – Pentane). **^{1}H-NMR** (($(CD_3)_2SO$, 500 MHz): δ 9.81 (s, 1H, $\mathrm{NH_{teoc}}$), 8.44 (t, J = 5.7 Hz, 1H, $\mathrm{NH_{cysteamine}}$), 7.74 (d, J = 8.9 Hz, 2H, $\mathrm{CH_{phenyl}}$), 7.52 (d, J = 8.9 Hz, 2H, $\mathrm{CH_{phenyl}}$), 7.36 – 7.28 (m, 12H, $\mathrm{CH_{trityl}}$), 7.27 – 7.20 (m, 3H, $\mathrm{CH_{trityl}}$), 4.19 (t, J = 8.5 Hz, 2H, $\mathrm{CH_{2,teoc}}$), 3.22 (q, J = 6.6 Hz, 2H, $\mathrm{CH_{2,cysteamine}}$), 2.32 (t, J = 7.1 Hz, 2H, $\mathrm{CH_{2,cysteamine}}$), 1.02 (t, J = 8.7 Hz, 2H, $\mathrm{CH_{2,teoc}}$), 0.05 (s, 9H, CH_3). **^{13}C-APT NMR** ($(CD_3)_2SO$, 126 MHz): δ 165.52 ($\mathrm{CO_{cysteamine}}$), 153.49 ($\mathrm{C_{q,phenyl}}$), 144.46 ($\mathrm{C_{q,trityl}}$), 142.04 ($\mathrm{CO_{teoc}}$), 129.06 ($\mathrm{CH_{trityl}}$), 128.05 ($\mathrm{CH_{phenyl}}$), 127.99 ($\mathrm{CH_{trityl}}$), 127.74 ($\mathrm{C_{q,phenyl}}$), 126.72 ($\mathrm{CH_{trityl}}$), 117.16 ($\mathrm{CH_{phenyl}}$), 65.90 ($\mathrm{C_{q,trityl}}$), 62.40 ($\mathrm{CH_{2,teoc}}$), 38.06 ($\mathrm{NC_{cysteamine}}$), 31.43 ($\mathrm{SC_{cysteamine}}$), 17.31 ($\mathrm{CH_{2,teoc}}$), -1.47 ($\mathrm{CH_{3,silyl}}$). HRMS $[M+Na]^+$ calculated for $[C_{34}H_{38}N_2O_3SSiNa]^+$: 605.24, found 605.23.

2-((*S*)-trityl)ethyl-(*N*)-4-aminebenzamido (8)



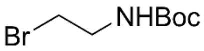
A 250 mL flask was charged with compound **7** (5.9 mmol, 3.5 g, 1.0 eq.) and anh. DMF (0.10 L, 55 mM) under a nitrogen atmosphere. TBAF (34 mL, 34 mmol, 5.8 eq., 1.0 M) was added and the mixture was stirred overnight. The reaction was quenched by water (0.12 L) and the formed suspension was evaporated. The obtained residue was dissolved in DCM (50 mL) and washed with sat. $NaHCO_3$ (aq.) (3x 20 mL) and water (5x 20 mL), dried over $MgSO_4$ and evaporated. Purification by silica column chromatography (7:3 EtOAc – Pentane) yielded compound **8** as a yellow solid (1.5 g, 3.5 mmol, 60%). R$_f$ = 0.48 (7:3 EtOAc – Pentane). **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ 7.57 (d, J = 8.6 Hz, 2H, CH$_{phenyl}$), 7.43 (d, J = 7.6 Hz, 6H, CH$_{trityl}$), 7.29 (t, J = 7.8, 6H, CH$_{trityl}$), 7.22 (t, J = 7.3 Hz, 3H, CH$_{trityl}$), 6.66 (d, J = 8.6 Hz, 2H, CH$_{phenyl}$), 6.16 (t, J = 5.9 Hz, 1H, NH), 3.97 (s, 2H, NH_2), 3.30 (q, J = 6.1 Hz, 2H, $CH_{2,cysteamine}$), 2.52 (t, J = 6.1 Hz, 2H, $CH_{2,cysteamine}$). **^{13}C-APT NMR** ($CDCl_3$, 126 MHz): δ 167.11 (CO$_{cysteamine}$), 149.37 (C$_{q,phenyl}$), 144.78 (C$_{q,trityl}$), 129.64 (CH$_{trityl}$), 128.81 (CH$_{phenyl}$), 128.06 (CH$_{trityl}$), 126.93 (CH$_{trityl}$), 124.49 (C$_{q,phenyl}$), 114.40 (CH$_{phenyl}$), 66.93 (C$_{q,trityl}$), 38.49 (NC$_{cysteamine}$), 32.53 (SC$_{cysteamine}$). **HRMS** (ESI) $[M+Na]^+$ calculated for $[C_{26}H_{26}N_2OSNa]^+$: 461.18, found 461.17.

2-mercaptoethyl–(*N*)-4-aminebenzamido (9)



Compound **8** (0.44 g, 1.0 mmol, 1.0 eq.) was dissolved in DCM (56 mL, 18 mM) and TFA (28 mL), H_2O (2.7 mL) and TES (2.7 mL) were added subsequently. The resulting mixture was left to stir for one hour. The mixture was evaporated and co-evaporated with toluene (3x). Purification by silica column chromatography (1:9 MeOH – DCM) provided TFA salt compound **9** (0.27 g, 0.88 mmol, 88%) as a yellow oil. R$_f$ = 0.21 (6:4 EtOAc – Pentane).**^{1}H-NMR** ($(CD_3)_2SO$, 400 MHz): δ 8.33 (t, J = 5.7 Hz, 1H, NH), 7.66 (d, J = 8.6 Hz, 2H, CH$_{phenyl}$), 6.84 (s, 2H, NH_2), 6.74 (d, J = 8.6 Hz, 2H, CH$_{phenyl}$), 3.37 (q, J = 7.0 Hz, 2H, CH_2), 2.61 (q, J = 6.9 Hz, 2H, CH_2), 2.36 (t, J = 8.1 Hz, 1H, SH). **^{13}C-APT NMR** ($(CD_3)_2SO$, 101 MHz): δ 165.23 (CO), 147.09 (C$_{q,phenyl}$), 127.86 (CH$_{phenyl}$), 122.88 (C$_{q,phenyl}$), 113.94 (CH$_{phenyl}$), 41.77 (NC$_{cysteamine}$), 22.61 (SC$_{cysteamine}$). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_9H_{12}N_2OSH]^+$: 197.07, found 197.07.

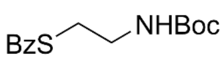
***tert*-butyl (2-bromoethyl)carbamate (11)**



An oven-dried 250 mL was charged with DCM (80 mL, 0.19 M) and Boc_2O (3.4 mL, 15 mmol, 1.0 eq.) and the mixture was cooled to 0 °C under a N_2 atmosphere. 2-Bromoethylamine (3.8 g, 19 mmol, 1.3 eq.) was added in 1-portion followed by dropwise addition of NEt_3 (3.6 mL, 26 mmol, 1.7 eq.). The resulting mixture was allowed to warm up and stirred overnight. Thereafter, the mixture was diluted with DCM (80 mL) and the organic layer was washed with NH_4Cl (aq.) (3x 50 mL), sat. $NaHCO_3$ (aq.) (3x 50 mL), brine (3x 50 mL), dried over $MgSO_4$ and evaporated. This provided compound **11** as a crude light yellow oil in quantitative yield and was directly used without further purification. Removal of unreacted Boc_2O can be achieved by re-dissolving the crude in ethanol (0.12 L, 0.13 M) and adding imidazole (1.0 g, 15 mmol, 1.0 eq.). This is allowed to stir for one hour and afterwards the mixture is concentrated and re-dissolved in DCM (25 mL). This is washed with cold (0 – 5 °C) aq. 1% HCl (3x 20 mL), dried over $MgSO_4$ and evaporated.[50] R_f = 0.66 (2:8 Et_2O – Pentane). **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ 5.22 (s, 1H, NH)*, 3.41 (q, J = 6.6 Hz, 2H, CH_2), 3.35 (t, J = 6.8 Hz, 2H, CH_2), 1.34 (s, 10H, CH_3). **^{13}C-APT NMR** (CD_3Cl, 126 MHz): δ 155.62 (CO), 79.53 (C_q), 42.29 (CH_2), 32.39 (CH_2), 28.27 (CH_3). Spectral data were in accordance with those reported in literature.[51]

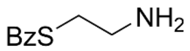
*Supposed to be a triplet but observed as mountain and therefore no J-coupling has been calculated.

***tert*-butyl (2-(*S*)-(thiobenzoate)ethyl)carbamate (12)**



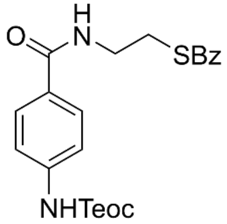
A 100 mL flask was charged with DMF (50 mL, 0.26 M), thiobenzoic acid (2.1 mL, 16 mmol, 1.2 eq.) and Cs_2CO_3 (2.8 g, 9.0 mmol. 0.65 eq.) under a nitrogen atmosphere. Compound **11** (3.0 g, 13 mmol, 1.0 eq.) was dissolved in DMF (17 mL, 0.76 M) and added dropwise to the solution. The resulting mixture was stirred overnight. The mixture was dissolved in Et_2O (80 mL) and washed with 2.5% $NaHCO_3$ (aq.) (3x 30 mL), water (3x 30 mL) and brine (3x 30 mL). The organic layer was dried over $MgSO_4$ and concentrated. Purification by silica column chromatography (2:8 Et_2O – Pentane) yielded compound **12** as a white solid (3.3 g, 12 mmol, 89%) over both steps. R_f = 0.41 (2:8 Et_2O – Pentane). **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ 7.94 (d, J = 8.4 Hz, 2H, CH_{bz}), 7.55 (d, J = 7.5 Hz, 1H, CH_{bz}), 7.42 (t, J = 8.2 Hz, 2H, CH_{bz}), 5.01 (t, J = 7.0 Hz, 1H, NH), 3.36 (q, J = 6.5 Hz, 2H, CH_2), 3.19 (t, J = 6.3 Hz, 2H, CH_2), 1.41 (s, 10H, CH_3). **^{13}C-APT NMR** (CD_3Cl, 126 MHz): δ 191.74 (CO_{bz}), 155.91 (CO_{boc}), 136.86 ($C_{q,bz}$), 133.59 (CH_{bz}), 128.68 (CH_{bz}), 127.33 (CH_{bz}), 79.50 ($C_{q,bz}$), 40.40 (NCH_2), 29.18 (SCH_2), 28.42 (CH_3). Spectral data were in accordance with those reported in literature.[52]

(*S*)-benzoylcysteamine (13)



A 100 mL flask was charged with compound **12** (3.3 g, 12 mmol, 1.0 eq.) and dissolved in 1:1 TFA – DCM (60 mL, 0.2 M). The resulting mixture was left to stir for one hour and concentrated. The remaining residue was co-evaporated with toluene to remove residual TFA. The resulting TFA salt, that is compound **13** (2.8 g, 9.8 mmol, 82%) and isolated as white powder, was directly used without further purification. R_f = 0.78 (1:19 MeOH – DCM). **^{1}H-NMR** (CD_3OD, 400 MHz) δ 8.00 (d, J = 8.5 Hz, 2H, CH_{bz}), 7.66 (t, J = 7.4 Hz, 1H, CH_{bz}), 7.53 (t, J = 7.9 Hz, 2H, CH_{bz}), 3.37 (t, J = 6.7 Hz, 2H, CH_2), 3.23 (t, J = 6.7, 2H, CH_2). **^{13}C-APT NMR** (CD_3OD, 101 MHz): δ 192.15 (CO), 137.90 ($C_{q,bz}$), 135.23 (CH_{bz}), 130.02 (CH_{bz}), 128.34 (CH_{bz}), 40.64 ($CH_{2,cysteamine}$), 26.94 ($CH_{2,cysteamine}$). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_9H_{11}NOSH]^+$: 182.06, found 182.06.

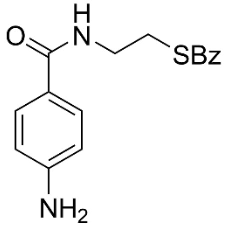
2-(*S*)-(benzothioate)ethyl–(*N*)-4-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)benzamido (14)



Compound **6** (2.7 g, 9.6 mmol, 1.0 eq.) was suspended in DCM (0.48 L, 20 mM). Thionyl chloride (12 mL, 0.16 mol, 17 eq.) and DMF (37 µL, 5.0 mol%) were added and the resulting mixture was refluxed at 55 °C for two hours. Completion of the reaction was confirmed by transferring a small sample into a LC-MS vial and adding acetonitrile and *n*-butylamine. The obtained mixture was then analyzed by LC-MS for the amide derivative. Once conversion to the acid chloride was confirmed the solution was cooled to room temperature and evaporated. Excess of $SOCl_2$ was removed by co-evaporation with toluene (3x). In a separate flask compound **13** (3.5 g, 12 mmol, 1.3 eq.) was dissolved in DCM (80 mL, 0.15 M) and cooled to 0 °C. DIPEA (4.2 mL, 24 mmol, 2.5 eq.) was added dropwise and the mixture was stirred for five minutes before the acyl chloride variant of **6** was added in portions to the solution. The mixture was stirred overnight and afterwards washed with sat. $NaHCO_3$ (aq.) (3x 50 mL). The organic layer was dried over $MgSO_4$ and evaporated. Purification by silica column chromatography (4:6 EtOAc – Pentane) provided compound **14** (2.6 g, 5.9 mmol, 61%) as a white powder. Traces of impurity where removed by suspending the powder in toluene and filtration. R_f = 0.49 (4:6 EtOAc –

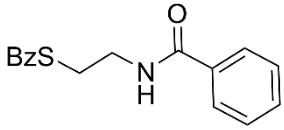
Pentane). **^{1}H-NMR** ($(CD_3)_2SO$, 500 MHz): δ 10.05 (s, 1H, NH), 8.73 (t, J = 5.1 Hz, 1H, NH), 7.90 – 7.81 (m, 4H, CH_{bz}, CH_{phenyl}), 7.63 (d, J = 8.7 Hz, 2H, CH_{phenyl}), 7.52 (t, J = 7.4 Hz, 1H, CH_{bz}), 7.46 (t, J = 7.4 Hz, 2H, CH_{bz}), 4.20 (t, J = 8.4 Hz, 2H, $CH_{2,cysteamine}$), 3.51 (q, J = 6.0 Hz, 2H, $CH_{2, cysteamine}$), 3.24 (t, J = 6.6 Hz, 2H, $CH_{2,cysteamine}$), 1.02 (t, J = 8.5 Hz, 2H, $CH_{2,teoc}$), 0.05 (s, 9H, CH_3). **^{13}C-APT NMR** ($(CD_3)_2SO$, 126 MHz): δ 189.33 (CO_{bz}), 166.28 ($CO_{cysteamine}$), 153.35 ($C_{q,phenyl}$), 144.58 (CO_{teoc}), 134.23 ($C_{q,bz}$), 131.19 (CH_{bz}), 130.03 ($C_{q,phenyl}$), 128.25 (CH_{phenyl}, CH_{bz}), 127.15 (CH_{bz}), 117.49 (CH_{phenyl}), 62.65 ($OCH_{2,teoc}$), 38.81 ($NCH_{2,cysteamine}$), 27.96 ($SCH_{2,cysteamine}$), 17.23 ($CH_{2,teoc}$), -1.51 (CH_3). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_{22}H_{28}Cl_3N_2O_4SSiH]^+$: 445.15, found 445.16.

2-(*S*)-(benzothioate)ethyl–(*N*)-4-aminebenzamido (15)



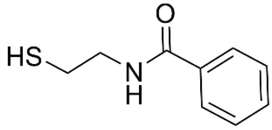
A 250 mL flask was charged with compound **14** (2.6 g, 5.8 mmol, 1.0 eq.) and anh. DMF (0.10 L, 55 mM) under a nitrogen atmosphere. TBAF (34 mL, 34 mmol, 1.0 M, 5.8 eq.) was added and the mixture was stirred overnight. The reaction was quenched by water (0.15 L) and Et_2O (0.15 L) was added. The organic layer was washed with sat. $NaHCO_3$ (aq.) (3x 0.10 L) and water (5x 0.10 L), dried over $MgSO_4$ and evaporated. Purification by silica column chromatography (6:4 EtOAc – Pentane + 1 % NEt_3) yielded a white solid crude. This was suspended in cold DCM and filtrated and the residue was washed with cold DCM (3x). This provided compound **15** (0.42 g, 1.4 mmol, 24%) as a white powder. $R_f = 0.58$ (6:4 EtOAc – Pentane). **^{1}H-NMR** (CD_3OD, 500 MHz): δ 7.80 (d, J = 7.9 Hz, 2H, CH_{bz}), 7.72 (d, J = 8.3 Hz, 2H, CH_{phenyl}), 7.51 (t, J = 7.5 Hz, 1H, CH_{bz}), 7.44 (t, J = 7.5 Hz, 2H, CH_{bz}), 6.62 (d, J = 8.3 Hz, 2H, CH_{phenyl}), 3.59 (t, J = 6.6 Hz, 2H, $CH_{2,cysteamine}$), 3.25 (t, J = 6.6 Hz, 2H, $CH_{2,cysteamine}$). **^{13}C-APT NMR** (CD_3OD, 126 MHz): δ 189.68 (CO_{bz}), 169.11 ($CO_{cysteamine}$), 154.29 ($C_{q,phenyl}$), 134.24 ($C_{q,bz}$), 131.36 (CH_{bz}), 129.34 (CH_{phenyl}), 128.22 (CH_{bz}), 126.97 (CH_{bz}), 124.99 ($C_{q,phenyl}$), 112.83 (CH_{phenyl}), 39.90 ($CH_{2,cysteamine}$), 27.39 ($CH_{2,cysteamine}$). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_{16}H_{16}N_2O_2SH]^+$: 301.09, found 301.10.

2-(*S*)-(benzothioate)ethyl–(*N*)-benzamido (18)



Compound **13** (3.7 g, 12 mmol, 1.2 eq.) was suspended in anh. DCM (67 mL, 0.15 M) and DIPEA (4.4 mL, 25 mmol, 2.5 eq.) was added. The resulting mixture was cooled to 0 °C and benzoyl chloride (1.2 mL, 10 mmol, 1.0 eq.) was added dropwise. This was let to stir overnight at room temperature. The mixture was diluted with DCM (0.10 L), washed with sat. $NaHCO_3$ (aq.) (3x 0.10 L), water (3x 0.10 L) and brine (3x 0.10 L), dried over $MgSO_4$ and concentrated. Purification by silica column chromatography (2:8 EtOAc – Pentane) provided compound **18** as a white powder (2.4 g, 8.3 mmol, 83%). $R_f = 0.34$ (2:8 EtOAc – Pentane). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ 7.97 (d, J = 8.6 Hz, 2H, CH_{phenyl}), 7.78 (d, J = 8.5 Hz, 2H, CH_{bz}), 7.59 (t, J = 7.5 Hz, 1H, CH_{bz}), 7.52 – 7.37 (m, 5H, CH_{bz}, CH_{phenyl}), 6.82 (t, 1H, NH), 3.76 (q, J = 5.8 Hz, 2H, CH_2), 3.36 (t, J = 6.0 Hz, 2H, CH_2). **^{13}C-APT NMR** ($CDCl_3$, 75 MHz): δ 192.88 (CO_{bz}), 167.71 (CO), 136.78 ($C_{q,bz}$), 134.30 ($C_{q,phenyl}$), 133.87 (CH_{bz}), 131.63 ($CH_{phenyl/bz}$), 128.83 ($CH_{phenyl/bz}$), 128.67 ($CH_{phenyl/bz}$), 127.46 (CH_{phenyl}), 127.08 (CH_{bz}), 40.56 ($CH_{2,cysteamine}$), 28.67 ($CH_{2,cysteamine}$). Spectral data were in accordance with those reported in literature.[53]

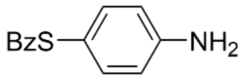
2-mercaptoethyl-(*N*)-benzamido (19)



Compound **18** (0.14 g, 0.50 mmol, 1.0 eq.) was suspended in dry MeOH (2.0 mL, 0.25 M) under a nitrogen atmosphere. A freshly prepared solution of NaOMe (3.0 mL, 0.2 M, 1.2 eq.) was added dropwise and the resulting mixture was stirred for two hours until TLC provided full conversion. The reaction mixture was neutralized (pH ≈ 7) by addition of Dowex H^+ resin. The resin was filtered off and washed with methanol. The residue was evaporated and purification by silica column chromatography (4:6 EtOAc – Pentane) to yield compound **19** (54 mg, 0.30 mmol, 60%) as white crystals. $R_f = 0.48$ (4:6 EtOAc – Pentane). **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ 7.78 (d, J = 8.0 Hz, 2H, CH_{phenyl}), 7.48 (t, J = 7.2 Hz, 1H, CH_{phenyl}), 7.40 (t, J = 7.9 Hz, 2H, CH_{phenyl}), 6.91 (s, 1H, NH), 3.60 (q, J = 6.3 Hz, 2H, CH_2), 2.75 (q, J = 7.5 Hz, 2H, CH_2), 1.40 (t, J = 8.5 Hz, 1H, SH). **^{13}C-APT NMR** ($CDCl_3$, 126 MHz): δ 167.75 (CO), 134.35 ($C_{q,phenyl}$), 131.68

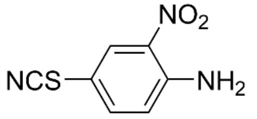
(CH_{phenyl}), 128.66 (CH_{phenyl}), 127.05 (CH_{phenyl}), 42.90 (NCH_2), 24.70 (SCH_2). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_9H_{11}NOSH]^+$: 182.06, found 182.06.

4-(*S*)-(benzothioate)aniline (20)



A 250 mL flask was charged with 4-aminothiophenol (1.3 g, 10 mmol, 1.0 eq.) and DCM (0.10 L, 0.1 M) under a nitrogen atmosphere. Upon cooling the solution 0 °C, NEt_3 (1.7 mL, 13 mmol, 1.3 eq.) was added. The mixture was stirred for ~five minutes before the dropwise addition of benzoyl-chloride (1.9 mL, 15 mmol, 1.5 eq.). TLC depicted full conversion of the starting material after four hours. The mixture was filtered and subsequently washed with sat. $NaHCO_3$ (aq.) (3x 0.10 L), water (3x 0.10 L) and brine (3x 0.10 L), dried over $MgSO_4$ and concentrated. Purification by silica column chromatography (3:7 EtOAc – Pentane) yielded compound **20** (0.47 g, 2.0 mmol, 20%) as vanilla colored crystals. R_f = 0.57 (3:7 EtOAc – Pentane). **^{1}H-NMR** (($(CD_3)_2SO$, 400 MHz): δ 7.95 (d, J = 8.6 Hz, 2H, CH_{bz}), 7.70 (t, J = 7.4 Hz, 1H, CH_{bz}), 7.57 (t, J = 8.0 Hz, 2H, CH_{bz}), 7.10 (d, J = 8.6 Hz, 2H, CH_{phenyl}), 6.64 (d, J = 8.6 Hz, 2H, CH_{phenyl}), 5.59 (s, 2H, NH_2). **^{13}C-APT NMR** $(CD_3)_2SO$, 126 MHz): δ 191.20 (CO), 150.50 ($C_{q,phenyl}$), 136.25 (CH_{phenyl}), 136.21 ($C_{q,bz}$) 133.96 (CH_{bz}), 129.21 (CH_{bz}), 126.93 (CH_{bz}), 114.45 (CH_{phenyl}), 109.66 ($C_{q,phenyl}$). Spectral data were in accordance with those reported in literature.[54]

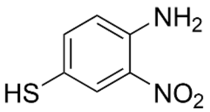
2-nitro-4-thiocyanatoaniline (21)



O-nitroaniline (8.3 g, 60 mmol, 1.0 eq.) was dissolved in acetic acid (0.10 L, 0.6 M) and sodium thiocyanate (NaSCN) (18 g, 0.24 mol, 4.0 eq.) was added under a nitrogen atmosphere. The solution was cooled to 0 °C and bromine (3.1 mL, 61 mmol, 1.0 eq.) in acetic acid (10 mL, 6.0 M) was added. The suspension was left to stir at 0 °C for two hours and afterwards cold water (0.45 L) was added. The suspension was filtered and washed with cold water (3x 0.20 L). The residue was collected and purification by silica column chromatography (4:6 EtOAc – Pentane) yielded compound **21** (8.5 g, 43 mmol, 73%) as a yellow solid. R_f = 0.17 (2:8 EtOAc – Pentane). **^{1}H-NMR** ($(CD_3)_2SO$, 500 MHz): δ 8.26 (s, 1H, CH_{phenyl}), 7.85 (s, 2H, NH_2), 7.64 (d, J = 8.6 Hz, 1H, CH_{phenyl}), 7.12 (d, J = 8.6 Hz, 1H, CH_{phenyl}). **^{13}C-APT NMR** $(CD_3)_2SO$, 126

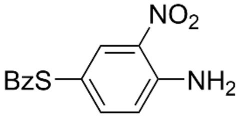
MHz): δ 147.15 ($C_{q,phenyl}$), 138.68 (CH_{phenyl}), 130.67 (CH_{phenyl}), 130.28 ($C_{q,phenyl}$), 121.43 (CH_{phenyl}), 112.26 ($C_{q,phenyl}$), 107.44 ($C_{q,thiocyanate}$). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_7H_5N_3O_2SH]^+$: 196.01 found 196.02.

2-nitro-4-thioaniline (22)



Compound **21** (0.57 g, 2.9 mmol, 1.0 eq.) was added portion wise to a cooled solution (0 ºC) of potassium hydroxide (KOH) (0.45 g, 8.0 mmol, 2.7 eq.) in ethanol (7.0 mL, 0.43 M) under a nitrogen atmosphere. The mixture was stirred for three hours at 0 °C, followed by addition of five% H_2SO_4 in ethanol until pH ≈ 5. The reaction mixture was poured into cold water (25 mL) and extracted with EtOAc (3x 10 mL). The combined organic layers were washed with brine (3x 10 mL), dried over $MgSO_4$ and evaporated. This yielded compound **22** as a red powder (0.27 g, 1.6 mmol, 55%) that was directly used without further purification. R_f = 0.43 (4:6 EtOAc – Pentane). **^{1}H-NMR** (($(CD_3)_2SO$, 400 MHz): δ 7.87 (d, J = 2.2 Hz, 1H, CH_{phenyl}), 7.74 (s, 2H, NH_2), 7.46 (dd, J = 8.9, 2.2 Hz, 1H, CH_{phenyl}), 7.04 (d, J = 8.9 Hz, 1H, CH_{phenyl}). **^{13}C-APT NMR** $(CD_3)_2SO$, 101 MHz): δ 146.70 ($C_{q,phenyl}$), 139.09 (CH_{phenyl}), 129.75 ($C_{q,phenyl}$), 129.50 (CH_{phenyl}), 120.86 (CH_{phenyl}), 120.53 ($C_{q,phenyl}$). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_6H_6N_2O_2SH]^+$: 171.01, found 171.02. Spectral data were in accordance with those reported in literature.[55] Most prevalent mass corelates to the disulfide 339.02.

4-(*S*)-(benzothioate)-2-nitroaniline (23)



Compound **22** (3.6 g, 21 mmol, 1.0 eq.) was initially dissolved in DCM (0.21 L, 0.1 M) under a nitrogen atmosphere. This was cooled to 0 °C and NEt_3 (3.9 mL, 28 mmol, 1.3 eq.) was added. After ~ five minutes benzoyl chloride (3.7 mL, 32 mmol, 1.5 eq.) was added and the mixture was left to stir for five hours at ambient temperature. Thereafter, it was filtered and the organic layer was washed with sat. $NaHCO_3$ (aq.) (3x 0.10 L), water (3x 0.10 L) and brine (3x 0.10 L). The organic layer was dried over $MgSO_4$ and evaporated. Purification by silica column chromatography (2:8 EtOAc – Pentane) gave compound **23** as a yellow powder (2.9 g, 11 mmol, 50%). R_f = 0.43 (2:8 EtOAc – Pentane). **^{1}H-NMR** (($(CD_3)_2SO$, 500 MHz): δ 8.07 (d, J = 2.2 Hz, 1H, CH_{phenyl}), 7.96 (dd, J = 8.5, 1.2 Hz, 2H, CH_{bz}), 7.79 (s, 2H, NH_2) 7.73 (t, J = 7.5 Hz, 1H, CH_{bz}), 7.59 (t, J = 7.8 Hz, 2H, CH_{bz}), 7.44 (dd, J = 8.9, 2.2 Hz, 1H, CH_{phenyl}), 7.12 (d, J = 8.9 Hz, 1H, CH_{phenyl}). **^{13}C-APT NMR** ($(CD_3)_2SO$, 126 MHz): δ 190.01 (CO), 146.93 ($C_{q,phenyl}$), 141.50 (CH_{phenyl}), 135.64 ($C_{q,bz}$), 134.35 (CH_{bz}), 132.43 (CH_{phenyl}), 130.35 ($C_{q,phenyl}$), 129.28 (CH_{bz}), 127.07 (CH_{bz}), 120.30 (CH_{phenyl}), 111.21 ($C_{q,phenyl}$). **HRMS** (ESI) $[M+H]^+$ calculated for $[C_{13}H_{10}N_2O_3SH]^+$: 275.04, found 275.04.

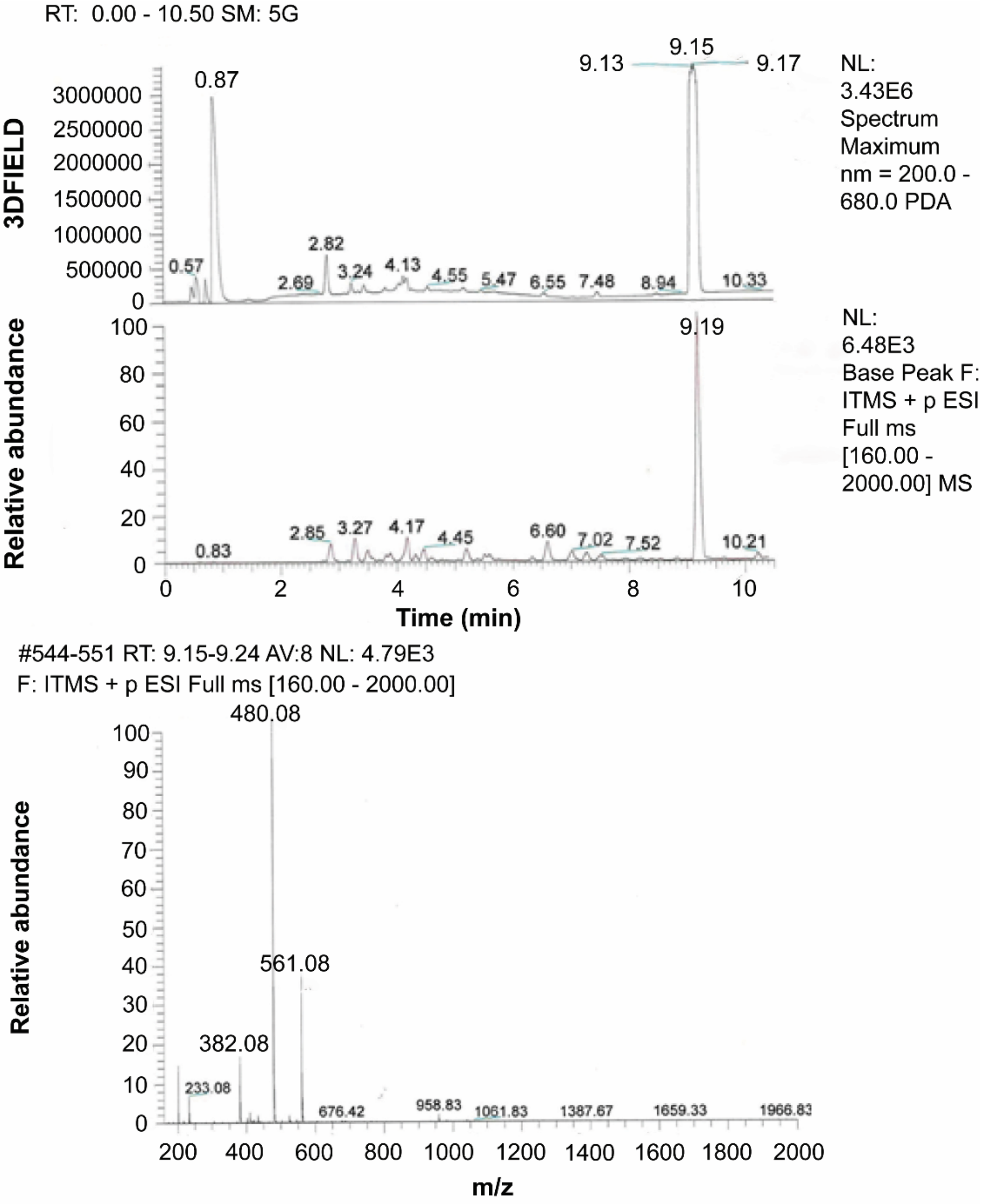


Figure S3.1. LC-MS spectrum of the reaction crude after performing the diazotization and C-H arylation with thiol 9.

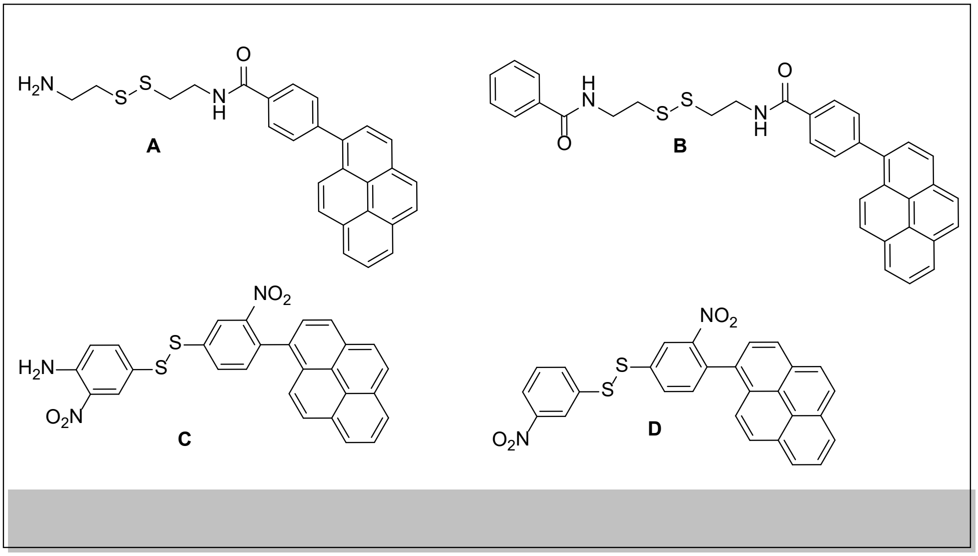


Figure S3.2. Overview of different by-products observed during the diazotization and C-H arylation with the different precursors.

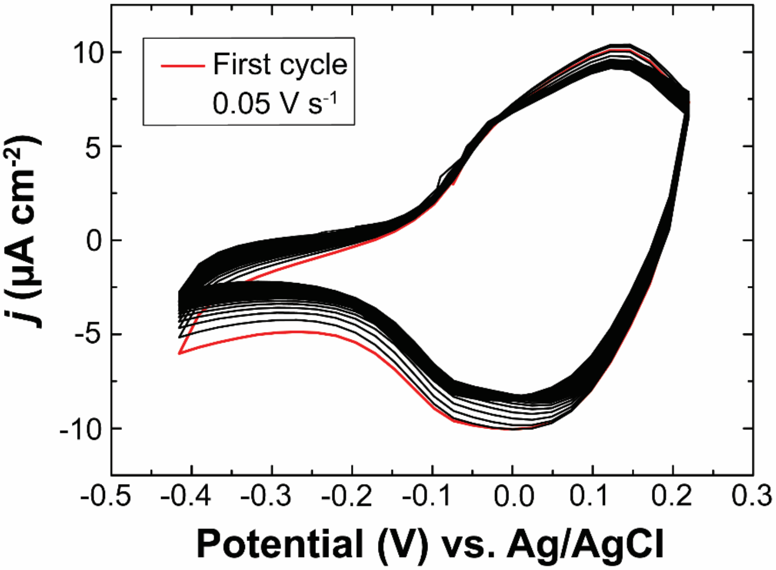


Figure S3.3. CV measurement of thiol linker 15. Measurements have been performed with Na_2SO_4, (0.1 M) in ultrapure water as electrolyte at a scan rate of 50 mV s^{-1}. Prior to addition the molecule was dissolved in 1.5% v/v acetonitrile. A total of 100 cycles have been conducted. Conditions: 1 atm, Ar, 293 K, platinum WE, gold rod CE and Ag/AgCl RE.

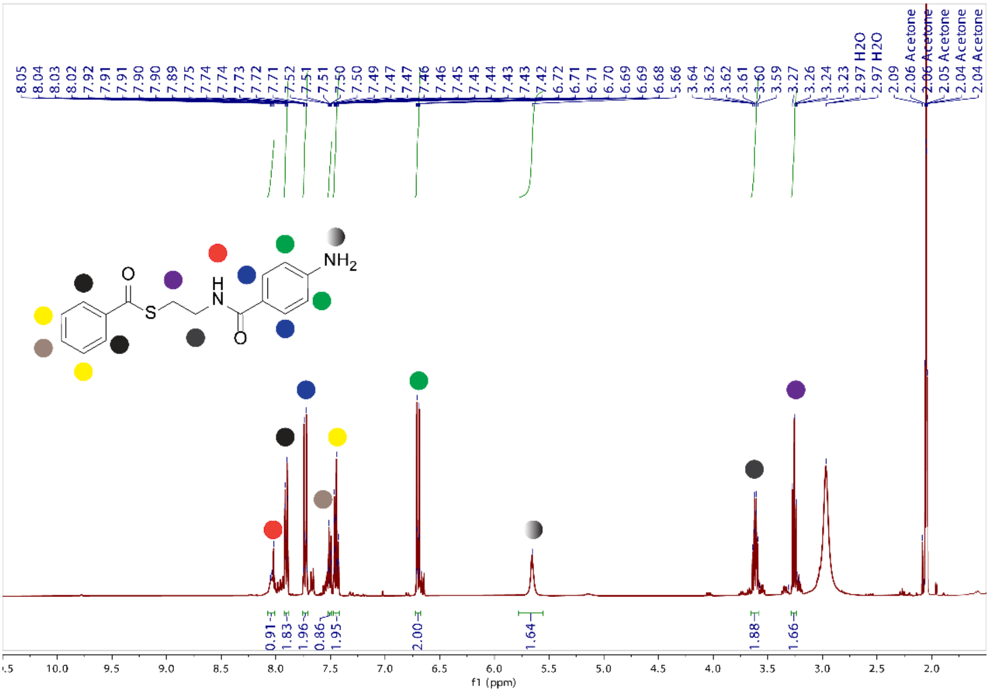


Figure S3.4. ^{1}H-spectrum of the Bz-protected thiol linker 15 after the CV measurement.

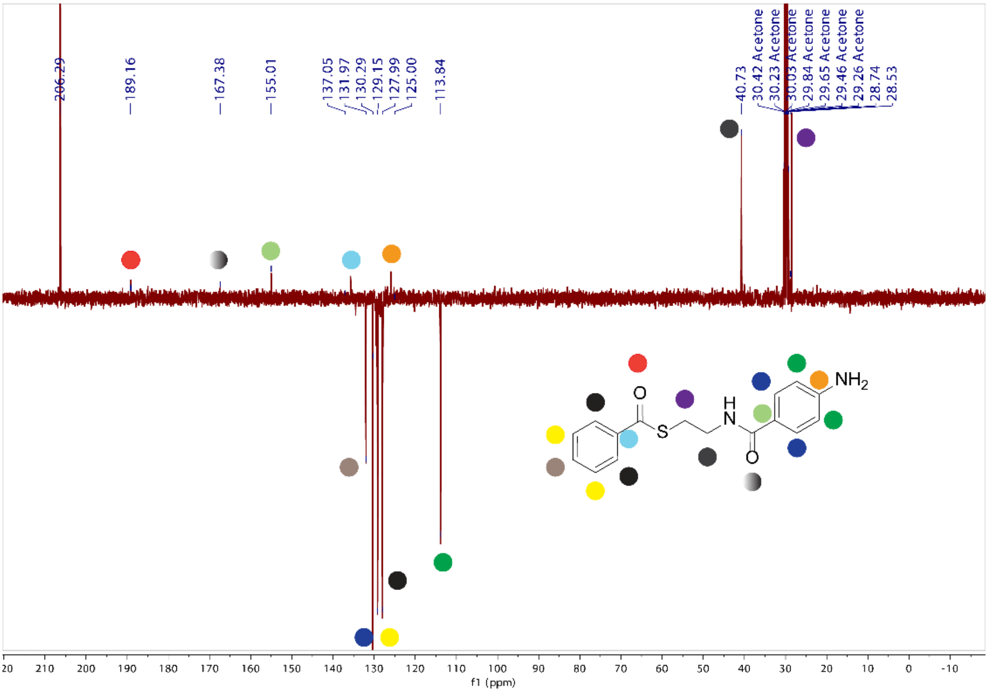


Figure S3.5. ^{13}C-APT spectrum of the Bz-protected thiol linker 15 after the CV measurement.

3.5 References

1. Hossain, M.Z. and N. Shimizu, *In situ functionalization of graphene with reactive end group through amine diazotization.* The Journal of Physical Chemistry C, 2017. **121**(45): p. 25223-25228.
2. Ren, R., et al., *Enhanced catalytic activity of Au nanoparticles self-assembled on thiophenol functionalized graphene.* Catalysis Science & Technology, 2015. **5**(4): p. 2149-2156.
3. Li, X., et al., *Preparation of graphene/copper composites with a thiophenol molecular junction for thermal conduction application.* New Journal of Chemistry, 2022. **46**(21): p. 10107-10116.
4. Greenwood, J., et al., *Covalent modification of graphene and graphite using diazonium chemistry: Tunable grafting and nanomanipulation.* ACS Nano, 2015. **9**(5): p. 5520-5535.
5. Sampathkumar, K., et al., *On the suitability of Raman spectroscopy to monitor the degree of graphene functionalization by diazonium salts.* The Journal of Physical Chemistry C, 2019. **123**(36): p. 22397-22402.
6. Wang, Q.H., et al., *Understanding and controlling the substrate effect on graphene electron-transfer chemistry via reactivity imprint lithography.* Nature Chemistry, 2012. **4**(9): p. 724-732.
7. Fan, X., R. Nouchi, and K. Tanigaki, *Effect of charge puddles and ripples on the chemical reactivity of single layer graphene supported by* SiO_2*/Si substrate.* The Journal of Physical Chemistry C, 2011. **115**(26): p. 12960-12964.
8. Romero-Muniz, C., et al., *Substrate-induced enhancement of the chemical reactivity in metal-supported graphene.* Physical Chemistry Chemical Physics, 2018. **20**(29): p. 19492-19499.
9. Long, B., et al., *Non-covalent functionalization of graphene using self-assembly of alkane-amines.* Advanced Functional Materials, 2012. **22**(4): p. 717-725.
10. Shown, I. and A. Ganguly, *Non-covalent functionalization of CVD-grown graphene with Au nanoparticles for electrochemical sensing application.* Journal of Nanostructure in Chemistry, 2016. **6**(4): p. 281-288.

11. Benvidi, A., et al., *Electrochemical deposition of gold nanoparticles on reduced graphene oxide modified glassy carbon electrode for simultaneous determination of levodopa, uric acid and folic acid.* Journal of Electroanalytical Chemistry, 2015. **736**: p. 22-29.
12. Zhao, G. and G. Liu, *Electrochemical deposition of gold nanoparticles on reduced graphene oxide by fast scan cyclic voltammetry for the sensitive determination of As(III).* Nanomaterials (Basel), 2018. **9**(1).
13. Shin, D., H.R. Kim, and B.H. Hong, *Gold nanoparticle-mediated non-covalent functionalization of graphene for field-effect transistors.* Nanoscale Advances, 2021. **3**(5): p. 1404-1412.
14. Zaniewski, A.M., C.J. Trimble, and R.J. Nemanich, *Modifying the chemistry of graphene with substrate selection: A study of gold nanoparticle formation.* Applied Physics Letters, 2015. **106**(12).
15. Park, Y., et al., *Spontaneous formation of gold nanoparticles on graphene by galvanic reaction through graphene.* ACS Omega, 2019. **4**(19): p. 18423-18427.
16. Bianco, G.V., et al., *Highly conductive and transparent graphene: Synergy of covalent and non-covalent co-doping.* Applied Surface Science, 2021. **564**: p. 150377.
17. Zaretski, A.V., et al., *Metallic nanoislands on graphene as highly sensitive transducers of mechanical, biological, and optical signals.* Nano Letters, 2016. **16**(2): p. 1375-1380.
18. Vacchi, I.A., C. Ménard-Moyon, and A. Bianco, *Chemical functionalization of graphene family members.* Physical Sciences Reviews, 2017. **2**(1): p. 20160103.
19. Khalil, I., et al., *Graphene–gold nanoparticles hybrid—synthesis, functionalization, and application in a electrochemical and surface-enhanced raman scattering biosensor.* Materials, 2016. **9**(6): p. 406.
20. Hong, S. and X. Li, *Optimal size of gold nanoparticles for surface-enhanced Raman spectroscopy under different conditions.* Journal of Nanomaterials, 2013. **2013**: p. 790323.
21. Schedin, F., et al., *Surface-enhanced Raman spectroscopy of graphene.* ACS Nano, 2010. **4**(10): p. 5617-5626.

22. Bottari, G., et al., *Chemical functionalization and characterization of graphene-based materials.* Chemical Society Reviews, 2017. **46**(15): p. 4464-4500.
23. Wei, T., et al., *Highly efficient and reversible covalent patterning of graphene: 2D-Management of chemical information.* Angewandte Chemie International Edition, 2020. **59**(14): p. 5602-5606.
24. Wetzl, C., et al., *The covalent functionalization of surface-supported graphene: An update.* Angewandte Chemie International Edition, 2023. **62**(6): p. e202212857.
25. Ismaili, H., et al., *Light-activated covalent formation of gold nanoparticle–graphene and gold nanoparticle–glass composites.* Langmuir, 2011. **27**(21): p. 13261-13268.
26. Cui, P., et al., *Nonvolatile memory device using gold nanoparticles covalently bound to reduced graphene oxide.* ACS Nano, 2011. **5**(9): p. 6826-6833.
27. Gam-Derouich, S., et al., *Design of molecularly imprinted polymer grafts with embedded gold nanoparticles through the interfacial chemistry of aryl diazonium salts.* Polymer, 2011. **52**(20): p. 4463-4470.
28. Liu, G., E. Luais, and J.J. Gooding, *The fabrication of stable gold nanoparticle-modified interfaces for electrochemistry.* Langmuir, 2011. **27**(7): p. 4176-4183.
29. Laurentius, L., et al., *Diazonium-derived aryl films on gold nanoparticles: Evidence for a carbon–gold covalent bond.* ACS Nano, 2011. **5**(5): p. 4219-4227.
30. Mesnage, A., et al., *Spontaneous grafting of diazonium salts: Chemical mechanism on metallic surfaces.* Langmuir, 2012. **28**(32): p. 11767-11778.
31. Paulus, G.L.C., Q.H. Wang, and M.S. Strano, *Covalent electron transfer chemistry of graphene with diazonium salts.* Accounts of Chemical Research, 2013. **46**(1): p. 160-170.
32. Hossain, M.Z. and N. Shimizu, *Covalent immobilization of gold nanoparticles on graphene.* The Journal of Physical Chemistry C, 2019. **123**(6): p. 3512-3516.

33. Crisóstomo, F.P., T. Martín, and R. Carrillo, *Ascorbic acid as an initiator for the Direct C-H arylation of (hetero)arenes with anilines nitrosated in situ.* Angewandte Chemie International Edition, 2014. **53**(8): p. 2181-2185.
34. Dixit, S., et al., *Ferrocene catalysed C–H arylation of arenes and reaction mechanism study using cyclic voltammetry.* Tetrahedron Letters, 2016. **57**(37): p. 4228-4231.
35. Elofson, R.M. and F. Gadallah, *Substituent effects in the polarography of aromatic diazonium salts.* The Journal of Organic Chemistry, 1969. **34**(4): p. 854-857.
36. Felipe-Blanco, D. and J.C. Gonzalez-Gomez, *Metal-free arylation-lactonization sequence of γ-alkenoic acids using anilines as aryl radical precursors.* European Journal of Organic Chemistry, 2019. **2019**(47): p. 7735-7744.
37. Fuchs, P.L., *Reagents for silicon-mediated organic synthesis*. 2011: John Wiley & Sons.
38. Giles, P.R. and C.M. Marson, *Dimethylchloromethyleneammonium Chloride*, in Encyclopedia of Reagents for Organic Synthesis (EROS). 2001.
39. Jiang, D.-e., B.G. Sumpter, and S. Dai, *How do aryl groups attach to a graphene sheet?* The Journal of Physical Chemistry B, 2006. **110**(47): p. 23628-23632.
40. Niyogi, S., et al., *Covalent chemistry for graphene electronics.* The Journal of Physical Chemistry Letters, 2011. **2**(19): p. 2487-2498.
41. Mysling, S., et al., *Electrochemical reduction of disulfide-containing proteins for hydrogen/deuterium exchange monitored by mass spectrometry.* Analytical Chemistry, 2014. **86**(1): p. 340-345.
42. Shahar, T., N. Tal, and D. Mandler, *The synthesis and characterization of thiol-based aryl diazonium modified glassy carbon electrode for the voltammetric determination of low levels of Hg(II).* Journal of Solid State Electrochemistry, 2013. **17**(6): p. 1543-1552.

43. Kaplan, A., et al., *Current and future directions in electron transfer chemistry of graphene.* Chemical Society Reviews, 2017. **46**(15): p. 4530-4571.

44. Alvarado, A., J.d. Deleija, and J.J. Gutierrez, *Synthesis of alkylthio benzene derivatives via simultaneous diazotization and nucleophilic displacement.* Results in Chemistry, 2021. **3**: p. 100227.

45. Mooste, M., et al., *Electrografting and morphological studies of chemical vapour deposition grown graphene sheets modified by electroreduction of aryldiazonium salts.* Electrochimica Acta, 2015. **161**: p. 195-204.

46. Kubota, K., et al., *Redox reactions of small organic molecules using ball milling and piezoelectric materials.* Science, 2019. **366**(6472): p. 1500-1504.

47. Xi, W., et al., *Clickable nucleic acids: Sequence-controlled periodic copolymer/oligomer synthesis by orthogonal thiol-X reactions.* Angewandte Chemie International Edition, 2015. **54**(48): p. 14462-14467.

48. Bulut, S. and W.L. Queen, *Catalyst-free synthesis of aryl diamines via a three-step reaction process.* The Journal of Organic Chemistry, 2018. **83**(7): p. 3806-3818.

49. Mullick, D., et al., *Carbamic acid 2-trimethylsilylethyl ester as a new ammonia equivalent for palladium-catalyzed amination of aryl halides.* Tetrahedron Letters, 2010. **51**(46): p. 5984-5987.

50. Basel, Y. and A. Hassner, *Imidazole and trifluoroethanol as efficient and mild reagents for destruction of excess di-tert-butyl dicarbonate [(BOC)2O].* Synthesis, 2001. **2001**(04): p. 0550-0552.

51. van Dijk, M., et al., *Synthesis and characterization of enzymatically biodegradable PEG and peptide-based hydrogels prepared by click chemistry.* Biomacromolecules, 2010. **11**(6): p. 1608-1614.

52. Lu, G.-p. and C. Cai, *An odorless, one-pot synthesis of thioesters from organic halides, thiourea and benzoyl chlorides in water.* Advanced Synthesis & Catalysis, 2013. **355**(7): p. 1271-1276.

53. Arisawa, M., T. Yamada, and M. Yamaguchi, *Rhodium-catalyzed interconversion between acid fluorides and thioesters controlled*

using heteroatom acceptors. Tetrahedron Letters, 2010. **51**(47): p. 6090-6092.

54. Wang, Q., et al., *Metal-free thioesterification of amides generating acyl thioesters.* New Journal of Chemistry, 2019. **43**(24): p. 9384-9388.

55. Schmidt, A., A.G. Shilabin, and M. Nieger, *On benzo[b][1,4]diazepinium-olates, -thiolates and -carboxylates as anti-Hückel mesomeric betaines.* Organic & Biomolecular Chemistry, 2003. **1**(23): p. 4342-4350.