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Direct organocatalytic enantioselective functionalization of SiO_x surfaces

John D. Parkin, Ross Chisholm, Aileen B. Frost, Richard G. Bailey, Andrew D. Smith*, and Georg Hähner*

Abstract: Traditional methods to prepare chiral surfaces involve either the adsorption of a chiral molecule onto an achiral surface, or adsorption of a species that forms a chiral template creating lattices with long range order. To date only limited alternative strategies to prepare chiral surfaces have been studied. In this manuscript a "bottom up" approach is developed that allows the preparation of chiral surfaces by direct enantioselective organocatalysis on a functionalized Si-oxide supported self-assembled monolayer (SAM). The efficient catalytic generation of enantiomerically enriched organic surfaces is achieved using a commercially available homogeneous isothiourea catalyst (HyperBTM) that promotes an enantioselective Michael-lactonization process upon a Si-oxide supported self-assembled monolayer functionalized with a reactive trifluoroenone group. Chiral atomic force microscopy (χ-AFM) is used to probe the enantiomeric enrichment of the organic films by measurement of the force distributions arising from interaction of D- or L-cysteine modified AFM tips and the organic films.

The generation of chiral surfaces is an area of widespread fundamental interest, finding varied applications as chiral selectors[1] (for example in HPLC to separate enantiomers),[2] in selective crystallisation,[3] and in enantioselective heterogeneous catalysis.[4] Chiral surfaces also play a central role in the life sciences and the study of biomaterials, as certain cell types are known to attach differentially to surfaces based on surface chirality, demonstrating sensitivity at the angstrom scale.[5] Chemical strategies to produce enantiomerically pure single-handed surfaces in a selective way are therefore highly desirable. The most common strategies to prepare chiral surfaces involve the adsorption of a chiral molecule onto an achiral surface that breaks symmetry and renders the surface chiral (Fig 1a). This is the approach adopted in the preparation of HPLC columns, and the postsynthetic modification of achiral MOFs with chiral units to produce chiral materials.[6] In a similar process, chiral homogeneous complexes or enzymes have also been covalently tethered to a surface (such as silica) in order to prepare enantioselective catalysts.[7] Cutting single crystals such that they exhibit high index faces is another method to produce a chiral surface.[8] While these "top down" approaches are well established, "bottom up" approaches that induce chirality directly on the surface are relatively rare. Within this area, the synthesis of chiral nanoparticles covered with organic molecules has been reported, where chirality arises from the arrangement of the ligands on the surface of the cluster cores.[9] In an alternative approach, chiral templating of an achiral surface with an asymmetric driving force such as a chiral seed leads to the assembly of achiral molecules into chiral structures (Fig 1b).[10] Another example has produced chiral surfaces through electrodeposition in a solution-based protocol that resembles biomineralization. In this process electrodeposition of a copper oxide film on an achiral gold surface in the presence of chiral tartrate salts in the deposition solution determined the chirality of the deposited film.[11]

We considered the feasibility of an alternative "bottom up" approach (Fig. 1c), which would allow the preparation of chiral organic surfaces by direct enantioselective catalysis on a functionalized Si-oxide supported self-assembled monolayer (SAM). This protocol is clearly distinct from the established types of chiral modification described previously. The successful demonstration of such a technique (i) provides the potential to diversify a functionalized achiral surface in a single step through a variety of catalytic enantioselective methods, and (ii) in principle could allow the preparation of high quality surfaces containing reactive functional groups that may be difficult to achieve using conventional deposition methods. In this manuscript, the proof-of-principle of this method is described. In this process an achiral carboxylic acid in solution is converted *in situ* (via a mixed anhydride) to a reactive chiral ammonium enolate using a chiral isothiourea catalyst that reacts with an achiral molecule adsorbed on the surface, creating a chiral organic surface. The enantiomeric enrichment of the resulting organic film is assessed using chiral atomic force microscopy (χ-AFM).

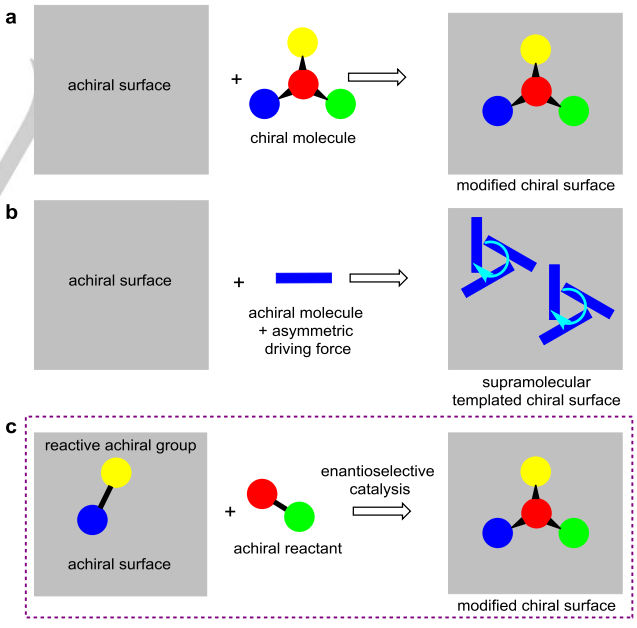

Figure 1: Common strategies to prepare chiral surfaces. **a** adsorption of chiral molecules onto an achiral surface; **b** adsorption of a species that forms a chiral template; **c** This work: enantioselective reaction on a surface.

Glass and silicon oxide substrates are important materials for biological applications[12] and the semiconductor industry. Functionalization of such surfaces has applications in electronics,[13] sensing,[14] and in micro- and nanoelectromechanical systems (MEMS and NEMS), with bespoke and selective functionalization of high importance.[15] Traditional methods reported for the functionalization of oxide

[*] J. D. Parkin, R. Chisholm, A.B. Frost, R.G. Bailey, A.D. Smith, G. Hähner
EaStCHEM School of Chemistry
University of St. Andrews
North Haugh
St. Andrews, KY16 9ST, UK

Email: ads10@st-andrews.ac.uk
gh23@st-andrews.ac.uk

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/ ….

surfaces use stoichiometric reactions between the surface and alkoxy- or allylsilanes, and are usually carried out at high temperatures and sometimes under harsh conditions.[16] The development of catalytic methods that offer facile and mild conditions for the functionalization of (oxide) surfaces are highly desirable. Modern enantioselective catalysis is a powerful method for the preparation of specific “single molecule” chiral building blocks with high efficiency. Organocatalysis has proven a useful tool for enantioselective carbon-carbon bond formation over the last decade, providing products with high levels of stereocontrol in solution. While this approach is generally applied to small molecule preparation, to the best of our knowledge the application of enantioselective catalysis to allow the direct generation of chiral surfaces formed of self-assembled monolayers (SAMs) has not been studied to date.

In previous work we have shown that trifluoromethylenone-terminated SAMs, bearing a reactive site for subsequent catalytic functionalization, can be readily prepared in a simple three-step procedure.[17] Catalytic functionalization of the enone-terminated SAM was achieved using an isothiourea-mediated organocatalytic Michael addition−lactonization process. Using an achiral isothiourea catalyst DHPB allowed the preparation of a variety of racemic lactone-terminated SAMs (in approximately 40-50% enone to lactone conversion) on SiO_x substrates that were characterized by XPS, ellipsometry, contact angle goniometry, and AFM.[18] In this manuscript both enantiomers of a chiral isothiourea, HyperBTM, are used to promote direct catalytic enantioselective functionalization of the trifluoromethylenone terminated surface (*via* the scheme in Fig 1c). The enantiomeric enrichment of an organic surface is generally difficult to detect using classical methods from organic or analytical chemistry such as HPLC, optical polarimetry, or circular-dichroism second harmonic generation spectroscopy (CD-SHG). However, atomic force microscopy (AFM) has proven a useful tool in the detection of different functional groups on surfaces since the mid 1990s,[19] operating through measuring the adhesive and friction forces between molecularly modified AFM probe tips and organic films with a suitable terminal functional group.[20] It can be applied to insulating films and substrates, in contrast to scanning tunnelling microscopy. While χ-AFM has previously been employed as a method for the enantiomeric discrimination of chiral surfaces prepared by adsorption of enantiopure substrates,[1, 21] in this manuscript the use of χ-AFM to interrogate the enantioselective functionalization of a surface is described.

Demonstration of the feasibility of probing enantiodiscrimination upon lactone terminated SAMs using χ-AFM was first performed, necessitating the adsorption of enantioenriched lactones of known enantiomeric ratio (er) onto the surface that would serve as a benchmarking standard. The synthesis of both antipodes of enantioenriched lactones **4** (Fig 2a) (>95:5 dr and 93:7 er) was achieved using an isothiourea mediated Michael-lactonization approach. Following methodology previously developed in solution,[17] *p*-F-phenylacetic acid **1** was treated with pivaloyl chloride to make the mixed anhydride *in situ*, followed by either enantiomer of the isothiourea catalyst HyperBTM **3** and *i*-Pr_2NEt as a surrogate base to promote catalytic enantioselective Michael-lactonization with alkyne-substituted trifluoromethyl enone **2**. After purification, the enantiomeric lactones (3*S*,4*S*)-**4** and (3*R*,4*R*)-**4** were each isolated in >95:5 dr and 93:7 er. The enantiomeric lactones (3*S*,4*S*)-**4** and (3*R*,4*R*)-**4** were subsequently attached to an azide terminated SAM *via* click methodology (see Fig 2a). The resultant chiral surfaces were characterized by water contact angle goniometry (CA) to determine the wettability, variable angle spectroscopic ellipsometry (VASE) to determine film thickness, X-ray photoelectron spectroscopy (XPS) to gather information about the chemical composition and conversion of azide to lactones, and AFM to determine the cleanliness and roughness of the films. In addition, AFM with chemically modified probes was employed for adhesion force measurements. RMS roughness values, film thickness and contact angle values confirmed the establishment of lactone terminated monolayers (for details see SI). As a representative example, XPS spectra obtained of the surface prepared from (3*R*,4*R*)-lactone (>95:5 dr, 93:7 er) are shown in figure 2b. The N 1s region was modelled with six peaks, three due to the residual azide (400.6 eV, 401.2 eV, 404.5 eV, green), and three due to the product triazole (399.9 eV, 400.6 eV, 401.9eV, blue).[22] The ratio of the intensities allows the conversion from the surface functionalized azide to the lactone to be estimated at ~82%. In the C 1s region six peaks/structures were fitted as diagramatically represented in Figure 2b. The experimentally determined and theoretical ratios of the individual peaks relative to the CF_3 peak are within experimental error and corroborate the preparation of a lactone terminated film (for details see SI). The

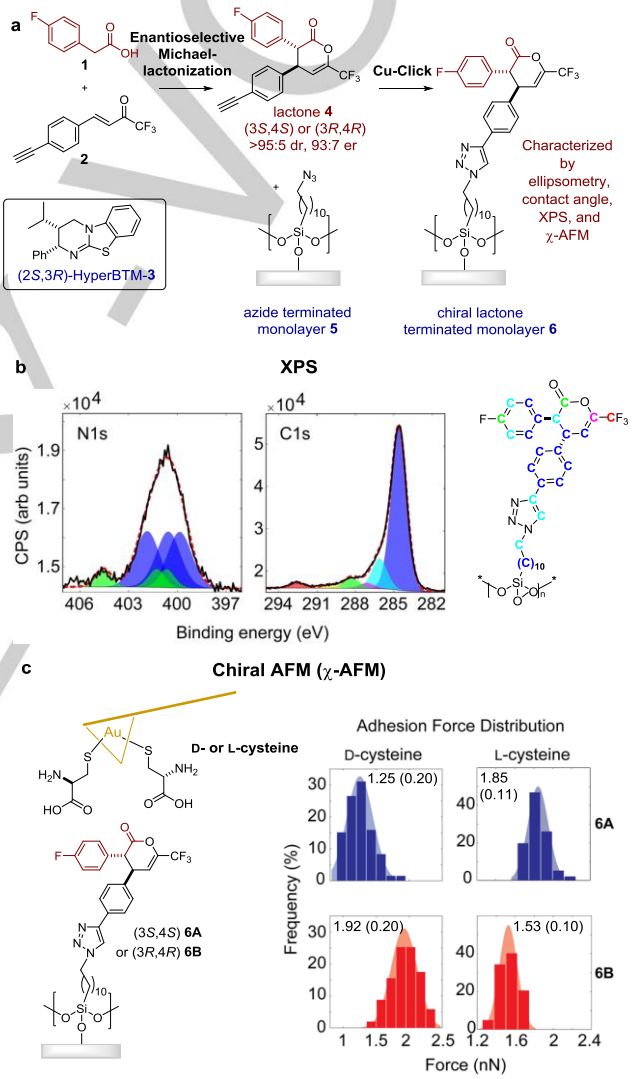

Figure 2: Enantiomerically enriched lactone surfaces prepared by click chemistry.
a Scheme of the Cu click reaction performed to produce an enantiomerically enriched lactone surface. **b** XPS N 1s and C 1s spectra of surface **6B** prepared by Cu-click adsorption of lactone (3R,4R)-**4** and color-coded structure of the adsorbed lactone. Black solid lines show the experimental data, the red dashed lines show the overall fit. Shaded areas are the indvidual peaks fitted (the structure is color coded according to the assigned C1s peaks-see SI for details). **c** AFM adhesion force distributions obtained from measurements performed with AFM probe tips modified with chiral cysteines and lactone terminated surfaces. Bars show experimental data. Shaded areas represent the best fit Gaussian distribution to the experimental data. Average adhesion forces (in nN) between chirally modified AFM tips and lactone terminated surfaces are also reported. The numbers in brackets are the standard deviations based on the distribution of the forces.

corresponding results for the (3*S*,4*S*) lactone-derived surface are very similar and are shown in the SI.

Subsequent investigations probed whether the adhesion values obtained from chiral atomic force microscopy could be used to discriminate between these chiral films derived from enantioenriched lactones. Firstly, AFM probes modified with enantiomerically pure D- and L-cysteine were prepared and tested for chiral discrimination, initially with cysteine modified Au-surfaces. The results confirmed that the quality of the chiral tips prepared was sufficiently high to allow for discrimination between enantiomers of simple chiral molecules (for details see SI). These tips were subsequently used in χ-AFM studies on the chiral surfaces prepared by click chemistry, with the same tips and surfaces used for comparison of the adhesion force measurements. Analysis of the adhesion values derived from the D-cysteine modified AFM tip with the (3*S*,4*S*)- and (3*R*,4*R*)-lactone adsorbed surfaces gave force distributions centred at 1.25 and 1.92 nN, respectively, consistent with clear enantiodiscrimination by χ-AFM (Figure 2c). Similarly, analysis of the adhesion values derived from the L-cysteine modified AFM tip with the (3*S*,4*S*)- and (3*R*,4*R*)-lactone adsorbed surfaces gave distributions centred at 1.85 and 1.53 nN.

Although distinct distributions are clearly observed from these stereoisomeric combinations, direct comparison of the absolute force values are non-trivial, as they are determined by the density of the lactone groups on the surface and of the cysteines on the tip, the roughness of surface and probe, and the actual contact area during adhesion measurement. Similarly, the width of the adhesion force distribution is in general determined by the homogeneity of the films on the AFM tip and the surface, the actual contact area between tip and surface, as well as the number of molecules involved in the interaction. However, the force distributions and values reported in Fig 2c provide strong evidence that the tip is mainly responsible for the observed widths of the distributions. This is most likely due to the roughness of the gold coating on the tip and the quality of the cysteine film, while the films on the SiO_x substrates are rather smooth and homogeneous, as shown by AFM. It has previously been reported that the width of the force distribution is influenced by the quality of the gold substrate and parameters such as grain size and roughness.[23] However, since the distribution of the adhesion forces follows the expected pattern when exchanging the chiral species on both probe and surface (the D-cysteine tip has a stronger interaction with the surface derived from (3*R*,4*R*)-**4,** while the L-cysteine tip had a higher affinity for the surface derived from (3*S*,4*S*)-**4**), the χ-AFM method is suited to identifying enantiomeric enrichment on these surfaces.

Having demonstrated that χ-AFM can be used to discriminate chiral surfaces of enantiomeric lactones adsorbed on a SiO_x surface, subsequent studies investigated the direct catalytic enantioselective modification of an enone functionalized SiO_x surface to prepare chiral lactones directly on the surface using HyperBTM **3** (Fig 3a). Separate samples of surface bound enone **7**, prepared from the corresponding azide and trifluoromethylenone **2,** were subjected to Michael-lactonization conditions using *p*-F-phenylacetic acid **1** and either enantiomer of the isothiourea HyperBTM (see Fig. 3a) or the achiral catalyst DHPB. The resulting surfaces showed properties similar to those prepared by direct adsorption through click chemistry, with details on contact angle measurements, film thickness and roughness reported in the SI. Representative XPS spectra for films prepared by Michael-lactonization with the chiral catalyst (2*S*,3*R*)-HyperBTM are shown in figure 3b. There is virtually no azide signal visible in the N 1s region at ~404.5eV. Therefore, we estimate the conversion from the azide to the enone to be >90%.[18]

An estimate of the conversion from the enone to lactone can be obtained from the ratio of the O=C-O/C-F signal (green) and the CF_3 signal (red), indicating ~37% conversion (for details see SI). A conversion of ~41% was observed when using the achiral catalyst DHPB.[18] XPS spectra for chiral surfaces prepared by Michael lactonization with catalyst (2*R*,3*S*)-HyperBTM are shown in the SI and gave very similar conversion from enone to lactone. These results indicate that the density of the lactone groups obtained through organocatalytic modification is approximately half that prepared by direct adsorption through Cu-click chemistry for the conditions used in the present study.

Adhesion force distributions obtained with D- and L-cysteine modified AFM tips on these surfaces prepared by either enantiomer of HyperBTM as well as the achiral catalyst DHPB are displayed in Figure 3c. The measured average adhesion forces and their standard deviations for the different chiral probes and surfaces are also reported.

Consistent with the chiral surfaces prepared through adsorption *via* click chemistry, these distributions indicate that the D-cysteine tip shows a stronger interaction with the surface prepared with (2*S*,3*R*)-HyperBTM [expected to be a surface functionalized with a (3*R*,4*R*)-lactone] while the L-cysteine tip has

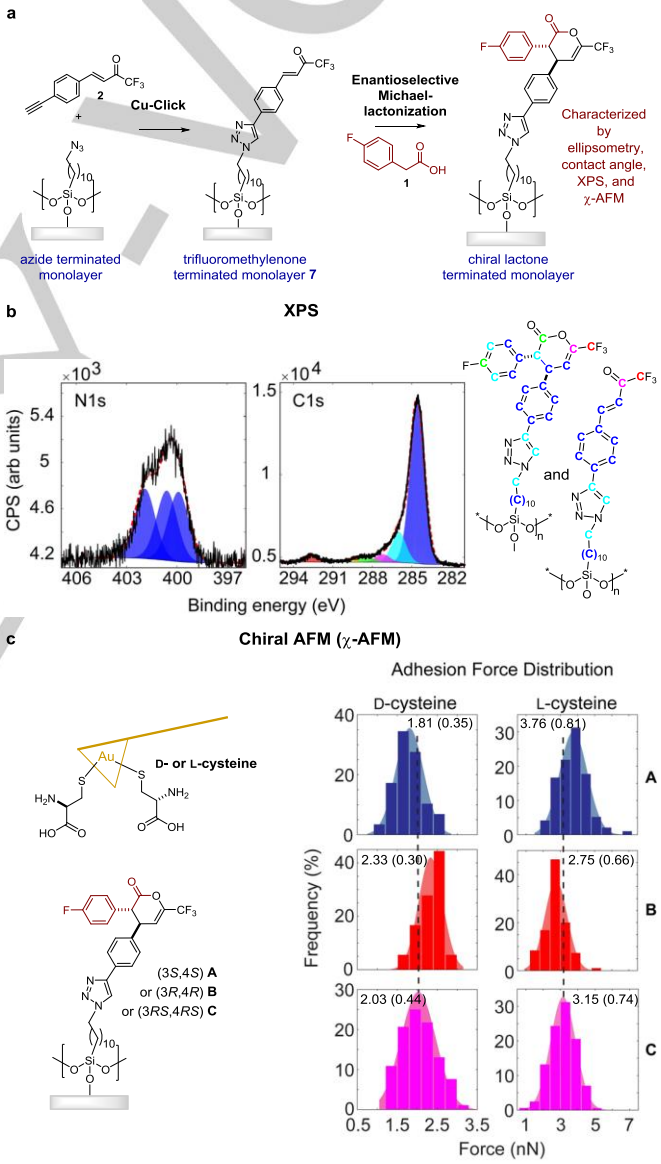

Figure 3: Enantioselective functionalization of a SiOx surface using isothiourea mediated organocatalysis.
a Scheme of the enantioselective organocatalytic reaction performed. **b** XPS N 1s and C 1s spectra of surface *(3R, 4R)* prepared by Michael lactonization and structures of the adsorbed enone and lactone molecules. **c** AFM L-and D-cysteine modified AFM tip evaluated against enantioenriched and racemic DHPs generated from the Michael addition-lactonization procedure using both enantiomers of HyperBTM **3** and achiral catalyst DHPB, respectively.

a higher affinity to the surface prepared using the antipode of HyperBTM. This strongly suggests that a diastereomeric interaction specific to the enantiomer of the chiral probe is responsible for the observed difference for a given AFM probe. The measured adhesion forces for the racemic surfaces prepared with the achiral catalyst DHPB lie between those observed for the films prepared with the chiral catalysts, supporting further that the adhesion is due to interactions between chiral surfaces. The results therefore provide strong evidence for discrimination due to chiral interactions between the tips and the surfaces, similar to the model system prepared via click chemistry, and indicate that enantioenrichment via organocatalytic preparation was achieved.

To conclude, in this work we report the first example of using organocatalytic enantioselective methodology to generate enantioenriched surfaces with a chiral catalyst to prepare chiral surfaces. The present results can initiate the production of two-dimensional chiral systems via organocatalysis and may afford opportunities for the preparation of a whole range of chiral surfaces with functionalities that are not accessible via other chemical methods. Such surfaces may be useful in chiral recognition processes, as templates for reactions or in separation applications. The present study demonstrates an easy and reliable route to obtain chiral surfaces with chemical functionality, by using a specific single-handed molecule (isothiourea HyperBTM **3**) that catalyzes the formation of a surface with desired chirality and functionality. Further ongoing work from within our laboratories is probing the scope and limitations of this methodology for the preparation of alternative bespoke chiral films as well as developing a method to quantitatively assess the level of enantioenrichment of the surfaces.

Experimental Section

Detailed information on materials and methods is available in the Supplementary Information. More detailed information on the surface analytical results obtained is also given in the SI.

Supplementary information and chemical compound information are available in the online version of the paper. The research data supporting this publication can be accessed at http://dx.doi.org/10.17630/4249dd27-5be0-47f2-999a-93f68f3831fe.

Acknowledgments

We thank the Engineering and Physical Sciences Research Council (GH, ADS and JDP acknowledge EP/K000411/1 and EP/L017008/1, and ADS and ABF acknowledge EP/J018139/1) and the Leverhulme Trust (GH and RGB acknowledge RPG-2015-109). This work was supported by the European Research Council under the European Union's Seventh Framework Programme (FP7/2007–2013) ERC grant agreement no. 279850. ADS thanks the Royal Society for a Wolfson Research Merit Award. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University, and the National EPSRC XPS Users' Service (NEXUS) Newcastle, UK, an EPSRC Mid-Range Facility.

Conflict of interest

The authors declare no conflict of interest.

Keywords: organic catalysis • heterogeneous catalysis • surface chemistry • chirality • scanning probe microscopy

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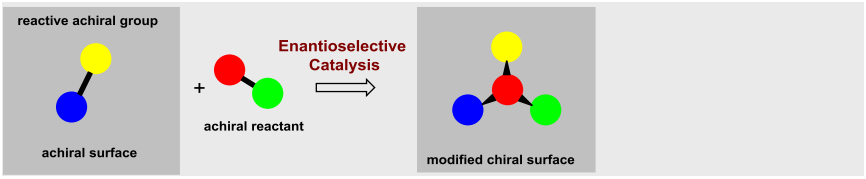

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