Click chemistry enables quantitative chiroptical sensing of chiral compounds in protic media and complex mixtures

F. Yushra Thanzeel, Kaluvu Balaraman & Christian Wolf

Click reactions have become powerful synthetic tools with unique applications in the health and materials sciences. Despite the progress with optical sensors that exploit the principles of dynamic covalent chemistry, metal coordination or supramolecular assemblies, quantitative analysis of complex mixtures remains challenging. Herein, we report the use of a readily available coumarin conjugate acceptor for chiroptical click chirality sensing of the absolute configuration, concentration and enantiomeric excess of several compound classes. This method has several attractive features, including wide scope, fast substrate fixation without by-product formation or complicate equilibria often encountered in reversible substrate binding, excellent solvent compatibility, and tolerance of air and water. The ruggedness and practicality of this approach are demonstrated by comprehensive analysis of nonracemic monoamine samples and crude asymmetric imine hydrogenation mixtures without work-up. Click chemosensing addresses increasingly important time efficiency, cost, labor and chemical sustainability aspects and streamlines asymmetric reaction development at the mg scale.
Chirality plays an essential role across the chemical and pharmaceutical sciences, and the development of new methods for the synthesis and analysis of chiral compounds are frequently required tasks in academic and industrial laboratories. To accelerate the discovery process, it has become routine to perform hundreds of small-scale reactions in parallel using widely available high-throughput experimentation equipment (HTE)\(^1\),\(^2\). With regard to asymmetric reaction development, many combinations of different chiral catalysts, solvents, additives, and other parameters typically need to be evaluated. In the search for an optimized procedure, a chemist can easily alter a large set of reaction parameters and produce hundreds of chiral samples in a very short time using multowell plate technology. In stark contrast with automated synthesis capabilities, the determination of the absolute configuration, yield, and enantiomeric excess of asymmetric reactions with traditional chromatographic methods that are serial in nature and incompatible with HTE remains slow, and this has shifted increasing attention to contemporary screening techniques\(^3\). Optical methods are compatible with parallel data acquisition, miniaturization, and multowell plate formats and offer a new path to real high-throughput analysis of chiral samples\(^4\)–\(^7\). Few examples of asymmetric reaction analysis with sensors operating on the principles of dynamic covalent chemistry\(^8\)–\(^11\), metal complex coordination\(^12\), and supramolecular chemistry\(^13\)–\(^15\) to recognize a chiral target compound and to generate quantifiable ultraviolet (UV), fluorescence, and circular dichroism (CD) signals have been reported\(^\text{16-18}\). Comprehensive chirality sensing (CCS), i.e., determination of the absolute configuration, yield, and enantiomeric excess (ee), of crude asymmetric reaction mixtures via irreversible covalent product fixation has been largely neglected to date\(^19\).

More than 10 years ago, Sharpless coined the term “click chemistry” for reactions that are high yielding, practical and operationally safe, avoid by-product formation, proceed in environmentally benign solvents at room temperature and generally under mild conditions, and eliminate chromatographic work-up\(^20\). Since then, a variety of reaction strategies and applications that exploit this concept, in particular in the biomedical domain, have been introduced\(^21\)–\(^28\). The inherently wide solvent compatibility is very attractive from an operational perspective because it simplifies adaptation to asymmetric reaction conditions, the nitro group at the CD intensity of the Michael addition/elimination product (see Supplementary Figures 8–13). The nitro group contribution results in a stronger and remarkably red-shifted CD signal which is advantageous for direct asymmetric reaction analysis because it eliminates interference from CD-active catalysts with the chiroptical measurements, vide infra. Although intramolecular hydrogen bonding (–NH–O2N–) is likely to occur with 7 in aprotic solvents it is not a prerequisite for this sensor to function. We obtained strong albeit quite different CD signatures using chloroform, dichloromethane, toluene, acetonitrile, and methanol, which is expected as the solvent choice can disturb the hydrogen bonding motif and alter conformational equilibria (Fig. 2, Supplementary Figures 14–16 and 28)\(^21\). In fact, intramolecular hydrogen bonding interactions are absent in the crystal structure of the primary amine addition product 7 and we observed very strong CD effects upon binding of substrates with secondary amine groups, for example 16, which affords a product devoid of an NH donor site (Figs. 1 and SI). The sensing does also not require CD coupling events and can therefore be applied to monofunctional aliphatic substrates such as 14–16. Altogether, these features result in a large scope which is highlighted by chirality sensing of 39 compounds. The inherently wide solvent compatibility is very attractive from an operational perspective because it simplifies adaption to asymmetric reaction conditions, for example when alcoholic co-solvents are used in catalytic enantioselective imine hydrogenations as described below. The sensing reaction and the corresponding CD effects were further investigated by UV, CD, and nuclear magnetic resonance (NMR) spectroscopy. We separately prepared the products of the reactions of 3 with 8, 17 and cis-22, respectively. The CDs of these isolated compounds match those generated in the sensing assays
The reaction between 1-phenylethylamine and probe 3 in the presence of Et₃N was closely monitored by ¹H NMR spectroscopy (Fig. 2). The spectra collected after 5, 10, and 15 min show the clean transformation of 3 and 8 into 7 which is complete after approximately 15 min at room temperature. For example, the signals at 1.39 ppm (H₄) and 4.12 ppm (H₆) of 8 undergo a downfield shift to 1.78 and 5.38 ppm, respectively, as 7 is formed. Accordingly, the doublet at 8.00 ppm (H₅) of probe 3 shows an upfield shift to 7.78 ppm in the reaction mixture.

The sensing with 3 exhibits the main elements of click chemistry: it is fast, wide in scope, displays smooth substrate binding with a coumarin Michael acceptor.
Probing with very high yield at room temperature, is compatible with a wide range of environmentally benign solvents such as methanol and acetonitrile, avoids formation of by-products, eliminates chromatographic or any type of work-up, is insensitive to air and moisture, and utilizes readily available starting materials, i.e., the coumarin probe \( \text{3} \) insensitive to air and moisture, and utilizes readily available products, eliminates chromatographic or any type of work-up, is insensitive to air and moisture, and utilizes readily available starting materials, i.e., the coumarin probe \( \text{3} \). We anticipated that these preferable reaction characteristics in combination with the distinct chiroptical readouts of the chiral amine derivatives of \( \text{3} \) and \( \text{7} \) would generate unique sensing opportunities.

**Comprehensive chirality and concentration sensing.** A closer look at the sensing of 1-(2-naphthyl)ethylamine, \( \text{10} \), revealed that the irreversible substrate binding concurs with a drastic UV increase at 265 and 355 nm, while the absorption at 309 nm remains unchanged (Fig. 3). This unique feature allows ratio-metric sensing of the amine concentration, for example by using the ratio of the relative absorption increase at 265 nm compared to the UV signal at 309 nm. We then conducted CD experiments and discovered that the induced CD maxima at 257 and 355 nm increase linearly with the substrate ee. The absolute configuration of \( \text{10} \) or another target compound can be assigned based on comparison of the sign of the induced CD signals with a reference and quantitative information about the substrate amount (concentration) and its enantiomeric composition is directly accessible from the UV changes and the CD amplitudes, respectively. This is particularly attractive because modern CD instruments generate UV and CD spectra simultaneously.

The robustness of the fast and quantitative Michael addition/elimination chemistry with a wide variety of chiral compounds in combination with the distinct chiroptical readouts of the coumarin sensor \( \text{3} \) suggested to us that sensing of complex mixtures, for example crude asymmetric reaction mixtures containing a variety of typically interfering compounds such as a chiral catalyst, additives, by-products and protic solvents, was within reach. We first decided to verify that the UV/CD responses...
Fig. 3 Chiroptical sensing of 10. a UV response of 3 to varying amounts of 10. b CD response of 3 to nonracemic samples of 10 and linear correlation between the induced CD signals at 257 (red) and 355 (blue) nm and the sample ee

Asymmetric reaction analysis. Finally, the chirality sensing method with chlorocoumarin 3 was applied to asymmetric reaction analysis (Table 2 and Supplementary Figures 75–80). We chose the iridium catalyzed hydrogenation of the N-methyl imine 48 to the secondary amine 17 for this purpose.\(^\text{36–40}\) Several ligands 49–53 and catalyst loadings were varied to determine the value of chiroptical sensing and to compare it with traditional NMR/chiral high-performance liquid chromatography (HPLC) analysis. The inherent ruggedness of our click chemistry sensing approach together with the wide solvent compatibility allowed us to simply take 200 µL aliquots from the methanolic reaction mixtures for direct UV/CD analysis. Based on a conservative estimate, the analysis time per sample was 60 min and 6 mL of solvent waste for diluting the samples were generated. The vast majority of the analysis time is required for the reaction of the amine product with the probe. If necessary this can be accelerated at higher temperatures, however, one can easily conduct hundreds of these experiments in parallel using multi-well plate technology. In such a high-throughput screening (HTS) scenario, the analysis of hundreds of reaction mixtures would still take approximately 1 hour.

We developed a chiral HPLC method with Boc-protected 17 to verify the results from our sensing assay. The traditional NMR and chiral HPLC analysis of the enantioselective imine hydrogenation required more than 7 h and 540 mL of solvent waste were accumulated, which can be mostly attributed to the formation and purification of the Boc-protected derivative 54. Overall, the results obtained by both methods are in good agreement. For example, the reaction with 5 mol% of the Phox ligand derived Ir catalyst gave (S)-17 in 55.8% ee and quantitative yield according to NMR and HPLC analysis which compares well to the 59.8% ee and 96.0% yield determined by sensing (entry 1). The error margins of the chiroptical sensing are fairly small and acceptable, in particular if one would apply the sensing assay to HTS of hundreds of samples. The minimization of time and chemical waste compared to traditional methods underscores the efficiency, practicality, cost and environmental sustainability advantages of chiroptical sensing with the coumarin 3.

In summary, we have developed a rugged click chemistry probe that allows comprehensive chirality sensing of a large variety of aliphatic and aromatic primary and secondary amines, amino alcohols, alcohols, and amino acids without the common shortcomings encountered with assays based on dynamic covalent chemistry, metal coordination, and supramolecular assemblies. The fast and irreversible substrate binding with readily available 4-halocoumarin sensors has several attractive features, including wide application spectrum, distinct chiroptical signaling at high wavelengths, operational simplicity, elimination
Table 1 UV/CD sensing of samples of 10 with varying concentrations and ee’s using 3

| Entry | Sample composition | Ratiometric sensing |
|-------|--------------------|---------------------|
|       | Abs. config. | Conc. (μM) | % ee | Abs. config. | Conc. (μM) | % ee (257 nm) | % ee (355 nm) | % ee (averaged) |
| 1     | R         | 4.00        | 25.0 | R            | 4.34        | 23.4 | 24.7 | 24.0 |
| 2     | R         | 2.25        | 55.5 | R            | 2.01        | 56.0 | 56.9 | 56.5 |
| 3     | S         | 5.00        | 50.0 | S            | 4.59        | 54.7 | 54.1 | 54.4 |
| 4     | R         | 9.20        | 8.0  | R            | 9.29        | 11.9 | 11.1 | 11.5 |
| 5     | S         | 2.50        | 33.3 | S            | 2.70        | 36.6 | 35.5 | 36.0 |
| 6     | R         | 7.00        | 42.8 | R            | 6.55        | 47.1 | 46.6 | 46.8 |
| 7     | S         | 8.00        | 37.5 | S            | 7.78        | 43.5 | 41.7 | 42.6 |
| 8     | S         | 9.75        | 79.0 | S            | 9.54        | 81.3 | 84.7 | 83.0 |
| 9     | S         | 1.25        | 60.0 | S            | 1.14        | 56.5 | 52.5 | 54.5 |

*Based on the sign of the CD response and comparison to a reference sample.
*Based on the UV response of the sensor.
*Based on the amplitude of the CD response.

Table 2 Analysis of the asymmetric hydrogenation of N-methyl-1-phenylethan-1-imine

1) Catalytic asymmetric imine hydrogenation

![Chemical structure of 48, 49, 50, 51, 52, 53, 54]

2) Reaction analysis

a) Chiroptical chirality sensing

17 + 3 → 54

Direct analysis of the crude reaction mixture without work-up.
Total solvent waste per analysis: 6 mL
Total time: 60 min

b) Traditional approach

Purification and N-Boc protection of 17 for chiral HPLC.
Total solvent waste per analysis: 540 mL
Total time: 7.3 h

| Entry | Reaction conditions | Traditional analysis | Chiroptical sensing |
|-------|---------------------|----------------------|--------------------|
|       | Ligand | Cat. load. (mol%) | Time (h) | Abs. config. | % ee | Conv. | Abs. Config. | % ee | Conv. |
| 1     | 49     | 5.00        | 18       | S         | 55.8 | 99.9 | S         | 59.8 | 96.0 |
| 2     | 50     | 5.00        | 18       | R         | 16.3 | 99.9 | R         | 14.3 | 99.9 |
| 3     | 51     | 5.00        | 18       | R         | 31.0 | 99.9 | R         | 32.2 | 99.1 |
| 4     | 52     | 5.00        | 18       | R         | 31.4 | 99.9 | R         | 25.8 | 98.0 |
| 5     | 53     | 5.00        | 18       | S         | 16.3 | 92.0 | S         | 14.2 | 96.3 |
| 6     | 49     | 2.50        | 1       | S         | 46.2 | 51.1 | S         | 47.8 | 53.9 |
| 7     | 49     | 3.25        | 1       | S         | 57.3 | 63.3 | S         | 54.5 | 68.4 |

*aThe enantiomeric excess and conversion were determined by chiral HPLC and 1H NMR.
*bThe enantiomeric excess and conversion were determined by CD and UV sensing at 376 and 392 nm, respectively. Cat. load.: catalyst loading, Conv.: conversion.
of by-product formation or complex dynamic equilibria, excellent solvent compatibility, and tolerance of air and water. The usefulness and practicality of this approach were demonstrated with the chiroptical sensing of the absolute configuration, concentration, and ee of several samples of 2-(2-naphthyl)ethylamine and by the direct analysis of crude reaction mixtures generated by iridium catalyzed asymmetric hydrogenation of a prochiral N-methyl imine to N-methyl 1-phenylethylamine, a challenging task for currently available sensing methods.

Compared to existing methodology, the practicality, robustness and scope of comprehensive click chirality sensing with 4-halocoumarin conjugate acceptors are remarkable. This strategy is uniquely effective and addresses increasingly important time efficiency and sustainability aspects by enabling reaction scale miniaturization and adaption to HTE, i.e., multiwell plate CD/UV analysis. The UV absorbance at 355 and 265 nm increased as the concentration of this solution, chloroform (2.0 mL) was added and the mixture was subjected to UV analysis. The UV spectrum was obtained as described above and the concentration was calculated using regression equations to determine the enantiomeric excess. The absolute configuration was determined using the sign of the CD effects (Table 1).

Asymmetric reaction analysis. Bis(1,5-cyclooctadiene)diiridium(I) dichloride ([Ir (cod)Cl]₂) (12.4 mg, 0.02 mmol) was added to the ligand, 49–53, (0.04 mmol) in dichloromethane and stirred for 30 min. N-Methyl-1-phenylethanimine-1-imine, 48, (100 mg, 0.75 mmol) and the preformed metal-ligand complex (0.04 mmol) were then combined in dichloromethane at 20 °C for 20 min and the mixture was stirred under 15 bar H₂ pressure overnight. To 200 μL of the crude reaction mixture, 4-chloro-3-nitroaniline, 3, (10.0 mM), and Et₃N (10.0 mM) were added in 2.0 mL of chloroform and stirred for 1 h. Then, 40 μL of this solution were diluted with 500 nm/min and a response of 1 s, using a quartz cuvette (1 cm path length). The data were baseline corrected and smoothed using a binomial equation.

Methods

General CD sensitivity procedure. To test the general utility of probe 3 as chirality probe, 20-31, 32-33, and 34-46 were used with chiral amines 4–6, 7, and tert-butyl dicarbonate was added to the filtrate. Due to the presence of methanol in the reaction mixture, di-tert-butyl dicarbonate was used in excess (3 equivalents) and the reaction was allowed to run for 5 h. Then the reaction mixture was concentrated and purified via flash column chromatography on silica using 10–40% dichloromethane in hexanes to afford N-Boc-N-methyl-1-phenylethylamine. The enantiomeric excess of N-Boc-N-methyl-1-phenylethylamine was determined by chiral HPLC using SS-Whelk-O1 as chiral stationary phase unless otherwise noted. Mobile phase: hexanesIPA = 99:1, flow rate = 1.0 mL/min, UV = 214 nm, t₁/₂ = 8.6 min (major) and t₂/₂ = 9.6 min (minor).

Data availability

The data that support the findings of this study are available from the corresponding author upon request. The X-ray crystallographic coordinates for 4-chlorocoumarin, 1, 4-bromocoumarin, 2, 4-ido-nitrocoumarin, 5, (S)-3-nitro-4-cyclohexylamino-3″-nitro-3″-alkylcoumarins, 7, and (R)-3-nitro-4-[(3-N-tert-butyl)-1-phenylethyl]amino)coumarin, 55, reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 1853449, 1853447, 1853450, and 1853451. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: 5 September 2018 Accepted: 16 November 2018

Published online: 14 December 2018

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Acknowledgments
This work is dedicated to William H. Pirkle who was an extraordinary scholar, teacher, and mentor. We are grateful for financial support from the U.S. National Science Foundation (CHE-1464547 and CHE-1764135).

Author contributions
F.Y.T., K.B. and C.W. designed and conceived the experiments. F.Y.T. and K.B performed the experiments and F.Y.T. analyzed the data with input from K.B. and C.W. All authors discussed the results and wrote the paper.

Additional information
Supplementary Information accompanies this paper at https://doi.org/10.1038/s41467-018-07695-9.

Competing interests: The authors declare no competing interests.

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