

# Asymmetric Reaction Screening with a Click Chemistry Sensor

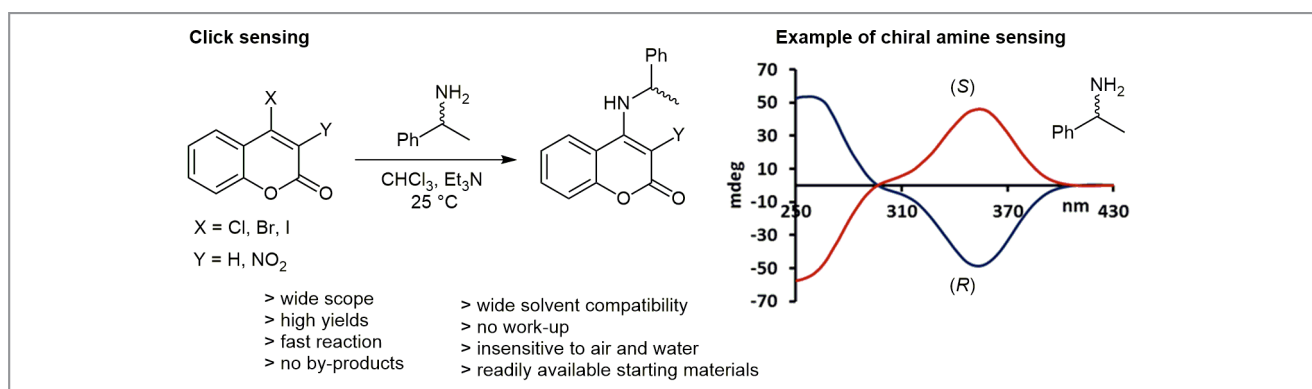
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The pace of scientific discoveries and developments in academic and industrial laboratories has reached staggering dimensions with the introduction and widespread use of generally available automated high-throughput experimentation equipment. “The full utilization of high-throughput screening (HTS) methodologies in asymmetric reaction development efforts, however, has been lagging behind for some time,” noted Professor Christian Wolf from Georgetown University (USA). “While hundreds of reactions can easily be conducted on the microscale using microwell plate technology, it is still quite a challenge to determine both yield and enantiomeric excess (*ee*) without product isolation or at least partial work-up”.<sup>1</sup> He added: “Recent advances with optical techniques that are compatible with parallel data generation from minute sample amounts are about to expand the toolbox of synthetic chemists. In the last few years, the chiroptical sensing field has left its ‘Mauerblümchen’ (‘wallflower’) image behind by shifting the focus to real-world applications.<sup>2,3</sup> As a result, increasingly practical molecular sensors that allow HTS of crude asymmetric reaction mixtures via UV, fluorescence or circular dichroism analysis have been developed and put to the test.”<sup>4</sup>

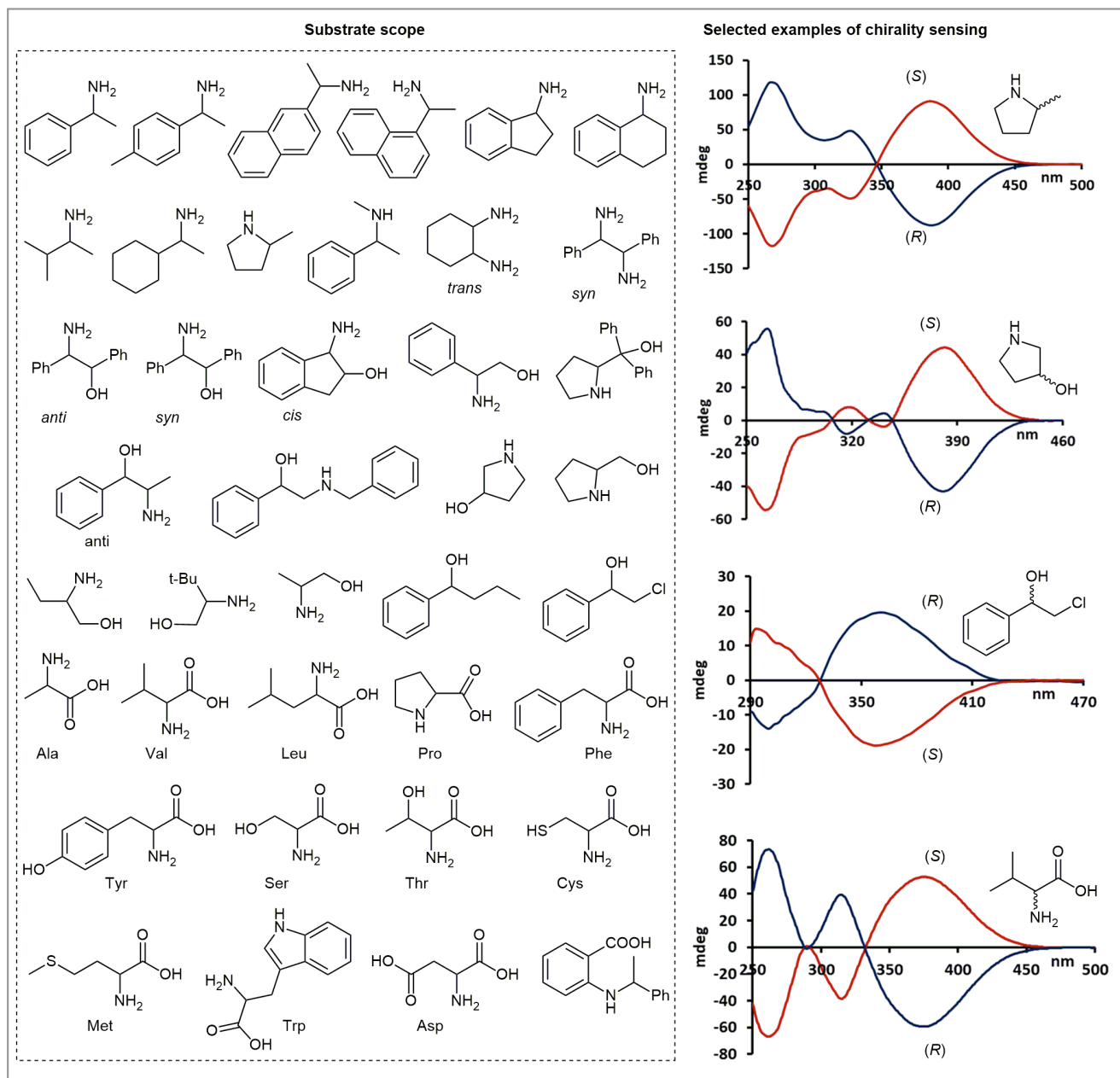
Direct yield and *ee* determination of asymmetric reactions requires a rugged assay that generates accurate data in the presence of possibly interfering chemicals, including starting materials, catalysts, reagents and by-products. To accomplish this challenging task, the group of Professor Wolf has now introduced an optical method with broadly applicable coumarin sensors exhibiting attractive click chemistry features.

Professor Wolf said: “In our search for a chromophoric sensor that is capable of direct asymmetric reaction screening, several 4-halocoumarins that can covalently bind a variety of nucleophilic target compounds were investigated. Proton NMR and UV studies performed with 4-chloro-3-nitrocoumarin and 1-phenylethylamine as analyte showed that this can be accomplished quantitatively in less than 15 minutes at millimolar concentrations and without by-product formation.” The group studied the performance of the sensor under various conditions to confirm broad solvent compatibility and tolerance of air and moisture. “Importantly, the substrate binding does not generate an additional stereogenic center,” explained Professor Wolf. He continued: “This facilitates the chiroptical analysis because it avoids complications that could arise from the formation of diastereomeric mixtures. The sensing event coincides with a colorimetric change and the formation of characteristic UV and CD signals allows concentration and *ee* analysis of the target compound. The optical click sensing assay is applicable to a wide variety of substrates including amines, amino alcohols, amino acids and alcohols (Scheme 2). We can use chloroform, dichloromethane, methanol or toluene as solvents and the sensing of amino acids can be performed in aqueous acetonitrile, which is attractive with regard to biological applications.”

With a rugged sensing assay in hand, the group attempted simultaneous *ee* and concentration analysis of nine scalemic samples of 1-(2-naphthyl)ethylamine by comparing the induced CD and UV spectra with calibration curves (Scheme 3). Professor Wolf said: “The absolute configuration of the major



**Scheme 1** Irreversible substrate binding with a click chemistry sensor

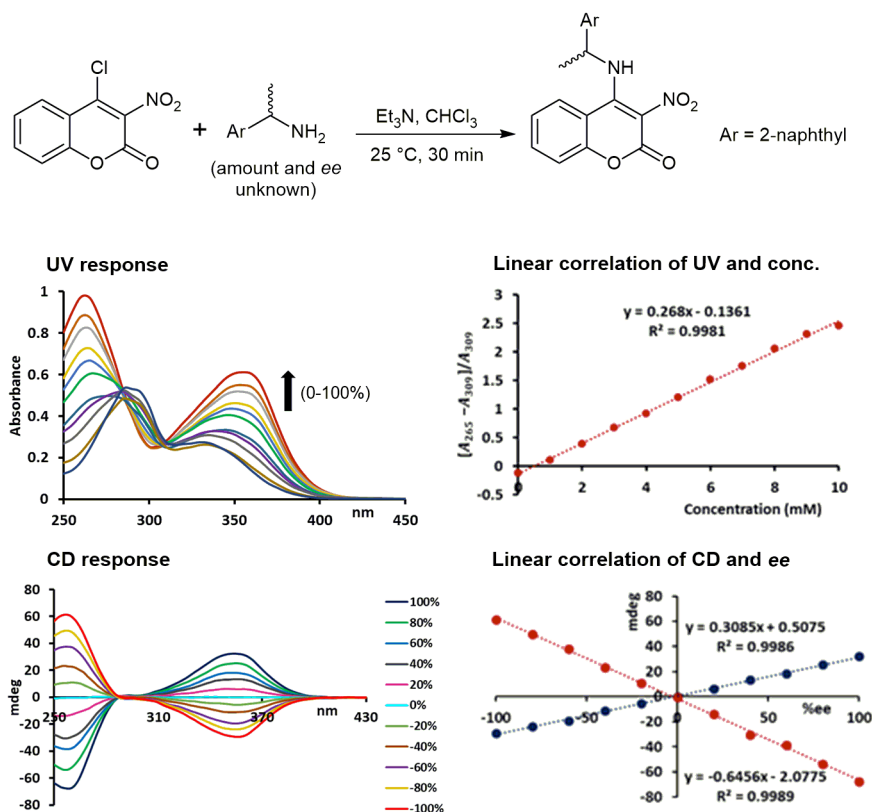


**Scheme 2** Target scope and selected examples of the distinct CD signals obtained at high wavelengths using 4-chloro-3-nitrocoumarin as sensor

enantiomer was assigned by comparison of the sign of the induced Cotton effect to a reference sample. Our click sensing gave accurate results in all cases. For example, the sensing of a sample containing (*R*)-1-(2-naphthyl)ethylamine in 4.00  $\mu\text{M}$  and 25.0% *ee* gave 4.34  $\mu\text{M}$  and 24.0% *ee* (Scheme 3, entry 1)."

Professor Wolf continued: "To determine the usefulness of our optical sensor in asymmetric reaction analysis, we

selected the iridium-catalyzed asymmetric hydrogenation of *N*-methyl-1-phenylethan-1-imine using several ligands with various catalyst loadings.<sup>5</sup>" The sensing was carried out with 200  $\mu\text{L}$  aliquots of crude reaction mixtures and the calculated conversion and *ee* obtained by chiroptical sensing were compared to traditional NMR and chiral HPLC analysis. The results were within a 5% error margin, which is generally considered

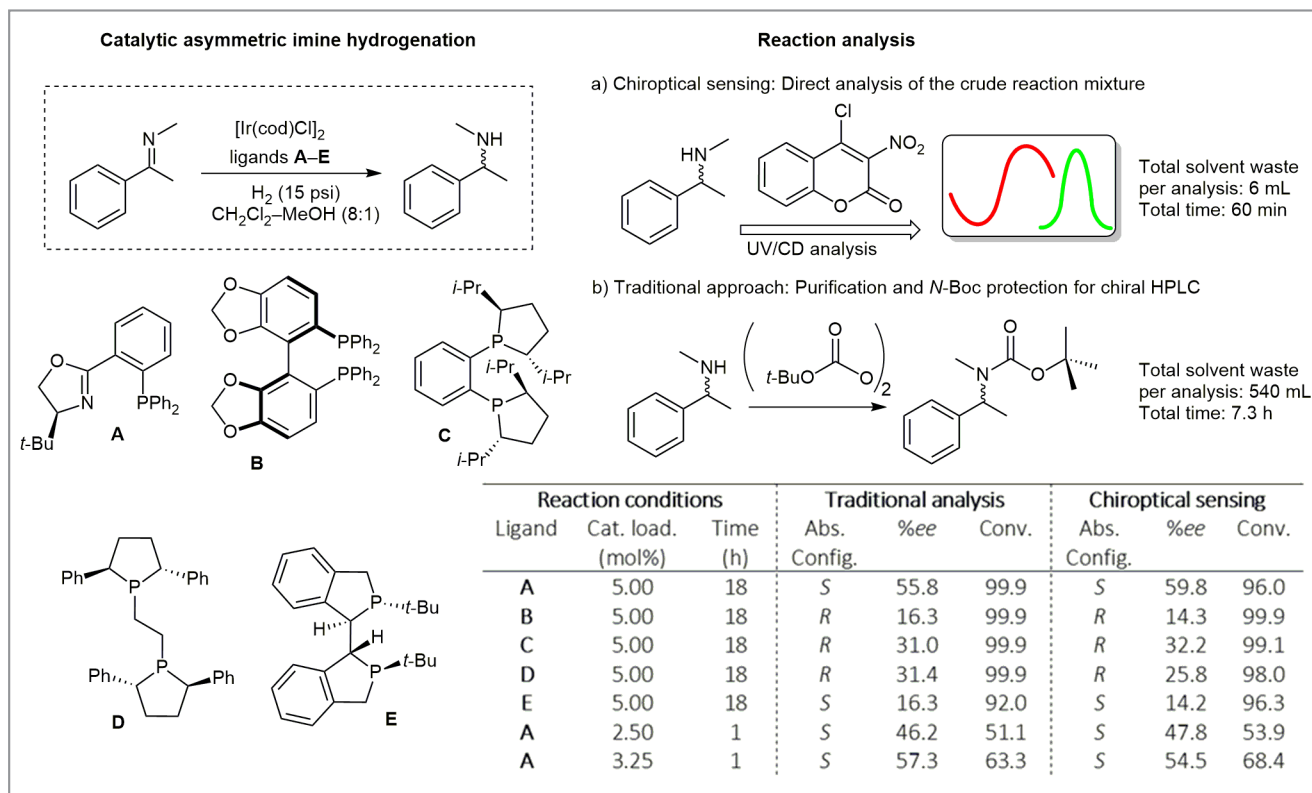


Entry	Sample composition			Sensing results				
	Abs. Config.	Conc. ( $\mu\text{M}$ )	%ee	Abs. Config.	Conc. ( $\mu\text{M}$ )	%ee (257 nm)	%ee (355 nm)	%ee (averaged)
1	R	4.00	25.0	R	4.34	23.4	24.7	24.0
2	R	2.25	55.5	R	2.01	56.0	56.9	56.5
3	S	5.00	50.0	S	4.59	54.7	54.1	54.4
4	R	9.20	8.0	R	9.29	11.9	11.1	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

**Scheme 3** UV and CD sensing of samples containing 1-(2-naphthyl)ethylamine in varying concentrations and ee's

acceptable for HTS applications. "Our optical assay is significantly faster and produces less waste than the traditional reaction analysis," remarked Professor Wolf, continuing: "The sensing assay generated approximately 6 mL of solvent waste per analyte and was complete within 1 hour while the traditional approach produced 540 mL and required more than 7 hours (Scheme 4)."

Professor Wolf concluded: "We have developed an efficient, robust optical method for quantitative chirality sensing of a wide range of substrates. Our coumarin sensor possesses attractive click chemistry features and was successfully applied to asymmetric reaction analysis utilizing only milligram quantities of the crude material. We have demonstrated that optical reaction analysis can be fast, and that it eliminates cumbersome purification steps and reduces chemical waste,



**Scheme 4** Analysis of the asymmetric hydrogenation of *N*-methyl-1-phenylethan-1-imine

time and labor. Altogether, optical chirality sensing with click chemistry coumarin probes offers new means to accelerate asymmetric reaction development efforts at reduced cost."

*Matthew Farnok*

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## About the authors



Dr. F. Y. Thanzeel

**F. Yushra Thanzeel** obtained her B.Sc in chemistry from the University of Peradeniya (Sri Lanka) in 2015. During her undergraduate studies, she worked with Prof. Ratnayake Bandara on alkaloid intercalation of *C. grandis* alkaloids into Montmorillonite (MMT) clay. She joined Prof. Christian Wolf's laboratory at Georgetown University (USA) in 2015 to pursue a Ph.D. During her first year of graduate school, she developed a substrate-specific sensing assay to quantify the concentration and enantiomeric composition of cysteine in biologically relevant media. In addition, her research comprises the design and synthesis of chiroptical sensors, chiral recognition studies, high-throughput screening, bio-conjugation and medicinal chemistry.



Dr. K. Balaraman

**Kaluvu Balaraman** graduated from Madurai Kamaraj University (India), with an M.Sc. in chemistry in 2007. He earned his Ph.D. in chemistry from IIT-Madras (India) in 2012 under the supervision of Prof. V. Kesavan, where he developed a novel class of tartaric acid derived bis(oxazoline) ligands for various asymmetric transformations. In 2013, he joined the group of Prof. Philippe M. Loiseau at the University of Paris Sud (France) for two years as a postdoctoral researcher in a CEFIPRA (Indo-French) project to investigate nanotechnology-based treatments of leishmaniasis. He continued working as a postdoctoral fellow (2015–2018) with Prof. Christian Wolf at Georgetown University (USA) where he developed new catalytic methodologies for the synthesis of fluorinated organic compounds. Currently, he is working as Assistant Research Professor at Georgetown University where he is playing a leading role in anticancer, Parkinson and Alzheimer drug development projects.



Prof. C. Wolf

**Christian Wolf** obtained his Ph.D. in 1995 from the University of Hamburg (Germany), working with the late Wilfried König on chiral biphenyls and cyclodextrin modifications. After postdoctoral work with the late William Pirkle at the University of Illinois (USA), he took an R&D position at SmithKline Beecham Pharmaceuticals (USA), in 1997. In 2000, he started as Assistant Professor at Georgetown University, Washington, DC (USA). He was appointed Associate Professor with tenure in 2006 and Full Professor in 2011. He has served as Director of the GU Medicinal Chemistry Shared Resource Center since 2017 and is cofounder of Enantiosense LLC. Current research interests include synthetic methodology, asymmetric catalysis, optical sensing methods, high-throughput screening, molecular recognition, stereodynamics of chiral compounds, cross-coupling reactions and medicinal chemistry aimed at the development of new treatments for cancer and brain diseases.