Organometallic Chirality Sensing via "Click"-like η⁶-Arene Coordination with an Achiral Cp*Ru(II) Piano Stool Complex

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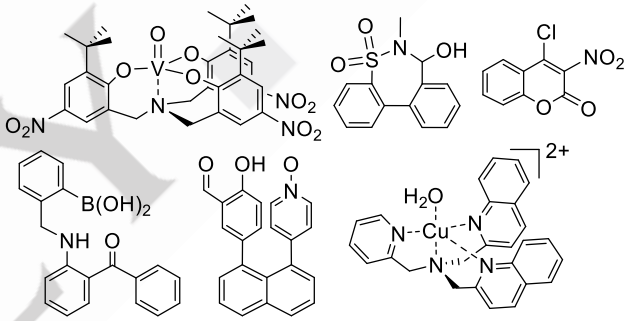
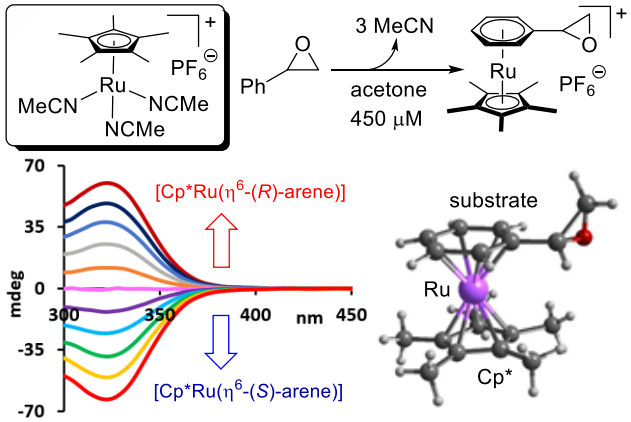
Abstract: Piano stool complexes have been studied over many years and found widespread applications in organic synthesis, catalysis, materials and drug development. We now report the first examples of quantitative chiroptical molecular recognition of chiral compounds through click-like η⁶-arene coordination with readily available half sandwich complexes. This conceptually new approach to chirality sensing is based on irreversible acetonitrile displacement of $[Cp^*Ru(CH_3CN)_3]PF_6$ by an aromatic target molecule, a process that is fast and complete within a few minutes at room temperature. The metal coordination coincides with characteristic circular dichroism inductions that can be easily correlated to the absolute configuration and enantiomeric ratio of the bound molecule. A relay assay that decouples the determination of the enantiomeric composition and of the total sample amount by a practical CD/UV measurement protocol was developed and successfully tested. The introduction of piano stool complexes to the chiroptical sensing realm is mechanistically unique and extends the scope of currently known methods with small-molecule probes that require the presence of amino, alcohol, carboxylate or other privileged functional groups for binding of the target compound. A broad application range including pharmaceutically relevant multifunctional molecules and the use in chromatography-free asymmetric reaction analysis are also demonstrated.

The synthesis and analysis of chiral compounds are pivotal and frequently required tasks across the chemical, materials and life sciences. High-throughput experimentation equipment routinely encountered in today's industrial and academic laboratories allows in-parallel production of hundreds of chiral samples in a short time. Unfortunately, this synthetic productivity is often slowed by analytical protocols despite the wide availability of automated pipetting systems and optical multi-well plate readers. This striking discrepancy continues to impede chiral compound development projects because the analytical bottleneck restricts throughput and ultimately limits the chemical space that can be explored. Chiroptical methods are perfectly amenable to automated high-throughput chiral compound screening platforms and chemometric data processing,[1-7] and are therefore primed to address this problem by avoiding costly and inefficient one-sample-at-a-time chromatographic sample analysis.[8,9] To this end, the chirality sensing realm has undoubtedly seen significant advances during the last few years.[10] Several challenges, maybe most notably the need to extend the application scope beyond traditionally studied compound classes, still lie ahead and require innovative solutions that carve out the full potential of this emerging field.

Previous work: *Small-molecule CD probes using conventional binding motifs for sensing of privileged compound classes*



This work: *New sensing space based on η⁶-arene binding with a Cp*Ru piano stool complex*



- Unique sensing motif and compound scope (>25 examples)
- Fast & practical optical chirality recognition (1-15 min)
- Continuous relay assay, red-shifted CD/UV inductions
- Determination of sample *er* & total concentration
- Stoichiometric (1:1) sensing, no analyte excess
- Sensitive, works at micromolar concentration
- Amenable to HTE equipment, eliminates chiral chromatography

Figure 1. State-of-the-art of chiroptical sensing. Representative examples of broadly useful small-molecule probes generally applied to alcohols, amines, amino acids, amino alcohols and carboxylates (top). The new senor design

represented by a ruthenium piano stool complex exploits η⁶-arene binding and eliminates dependence on traditionally targeted functional groups (bottom).

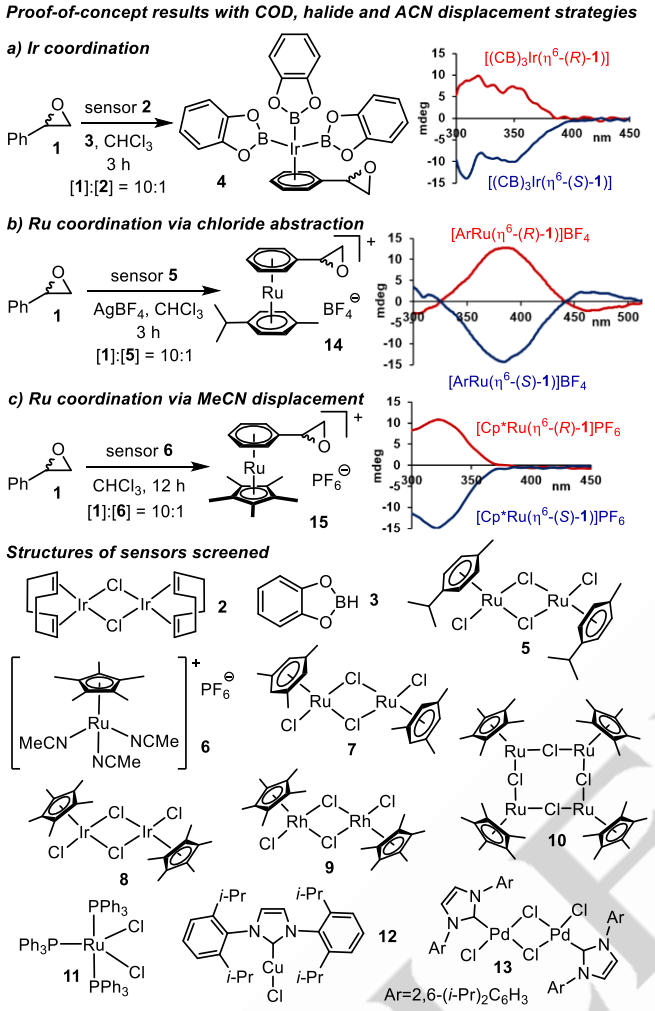


Figure 2. Chiroptical sensing development and initial proof-of-concept results. The CD inductions observed upon coordination of the *R*- and *S*-enantiomer of styrene oxide to the iridium or ruthenium complexes **2** (a), **5** (b) and **6** (c) are shown in red and blue, respectively (top). Structures of sensors examined (bottom). The ICD spectra of **4**, **14** and **15** were measured at 7.1, 12.5 and 21.6 mM in chloroform. CB=catecholboryl. See SI for details.

Many chiroptical sensing assays that allow chromatography-free analysis of privileged targets such as amines, amino alcohols, amino acids, diols and hydroxy acids have been introduced to date.[11-26] Chiral compounds typically display weak, blue-shifted UV and circular dichroism (CD) signals which precludes accurate concentration and *er* analysis, in particular when only small sample amounts are available. This intrinsic deficiency can be addressed by fast covalent or noncovalent attachment of a chromophoric probe when a suitable functional group, for example a primary amine or carboxylate that may be recognized via Schiff base formation[27-31] or hydrogen bonding interactions,[32-34] is available. Compounds devoid of an easily traceable functionality remain challenging and the general utility of chiroptical sensing is still mostly confined to the few compound classes mentioned above. As a result, methodically distinct and more generally applicable assays based on new sensing strategies are needed to expand the currently limited chirality sensing landscape. Noteworthy progress in this direction has been made with cucurbiturils, pillararenes, calixarenes and other macrocycles that can form CD-active inclusion complexes with chiral guests.[35-42] Unfortunately, the optical properties of these hosts are often unfavorable and produce weak CD maxima at short wavelengths below 300 nm. We now wish to introduce a conceptually new approach that overcomes these limitations through the use of a unique molecular recognition motif that has not been applied in the chirality sensing field to date.

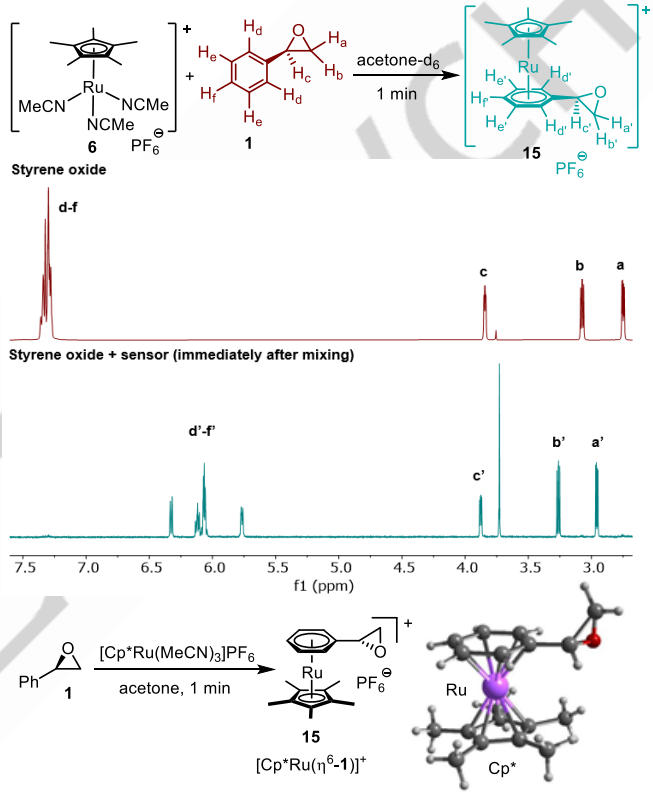


Figure 3. Sensing reaction analysis using $[Cp^*Ru(ACN)_3]PF_6$. Quantitative complexation of **1** at 25 °C is complete using stoichiometric amounts of **6** within one minute according to ^1H NMR analysis (top). The proposed η⁶-binding was confirmed by X-ray analysis of a single crystal of **15** (bottom).

Encouraged by our success with sensing of terpenes and terpenoids exhibiting a single double bond as the only functional group through late transition metal complexation,[43] we decided to explore the possibility of chirality sensing via η⁶-arene coordination since aromatic rings are frequently encountered in chiral compounds (Figure 1). Herein, we show that an achiral Cp*Ru(II) piano stool complex enables fast molecular recognition of a wide selection of chiral compounds at micro- or millimolar concentrations via spontaneous induction of characteristic CD signals. This overcomes the dependence of small-molecule sensors on traditionally targeted functional groups and streamlines chromatography-free analysis of the enantiomeric composition and overall concentration of many chiral molecules,

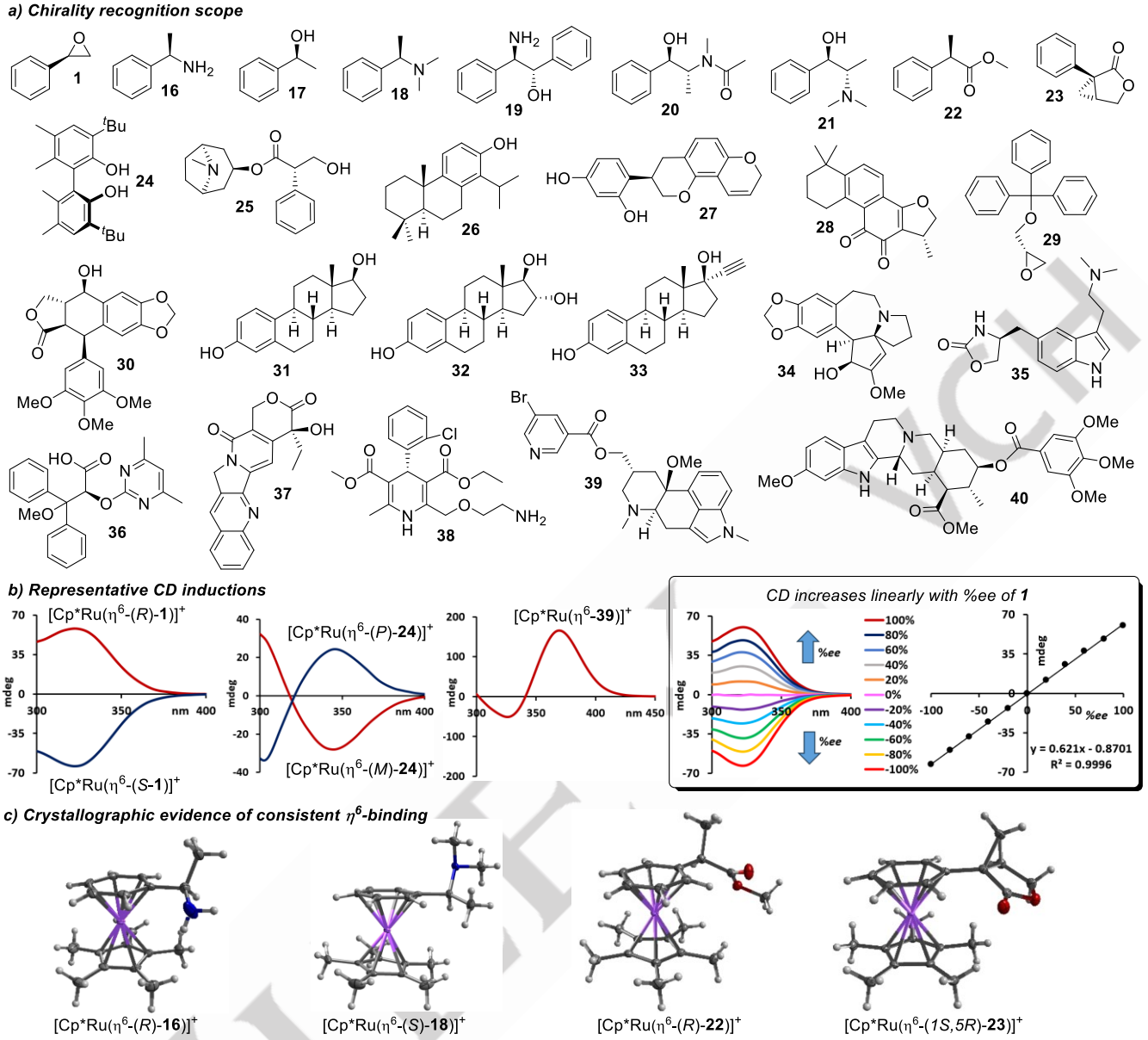


Figure 4. Scope of chirality sensing with the Cp*Ru(II) piano stool complex. Only one enantiomer of the target molecules is shown for clarity (a). Selected CD inductions and linear correlation of the ICD amplitudes and sample *ee* (b). Crystallographic evidence of the η^6-arene binding motif (c).

including complicated structures and pharmaceutically relevant targets.

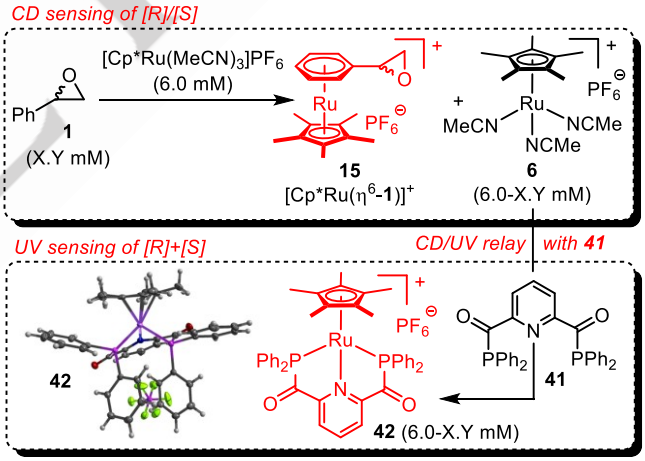
The fascinating structures, properties and catalytic applications of piano stool complexes have received considerable attention over many years.[44-46] At the onset of this study, we envisioned that η^6-complexation of chiral compounds would result in the generation of strong CD signals and thus provide an opportunity to extend the current utility of piano stools into the molecular recognition and chiroptical sensing realms. Inspired by (η^6-arene)Ir($C_6H_4BO_2$)$_3$ structures reported in the literature,[47] we sought to produce similar complexes using enantiopure styrene oxide, **1**, as our model compound. Indeed, the mixing of a 10-fold excess of either (*R*)- or (*S*)-styrene oxide with [IrCl(cod)]$_2$, **2**, and catecholborane, **3**, gave the assembly **4** showing a noticeable albeit still weak induced CD (ICD) effect above 300 nm (Figure 2a). With this first proof-of-concept result in hand and encouraged by the work from the Holman laboratory,[48-50] we then continued our screening efforts with several ruthenium, iridium, rhodium, copper and palladium complexes **5-13** that could possibly bind styrene oxide in similar ways after halide abstraction or acetonitrile displacement. The success of this strategy became evident when we used the dichloro(*p*-cymene)ruthenium(II) dimer **5** and silver tetrafluoroborate to form the η^6-styrene oxide complex **14** which

produced distinct ICD effects (Figure 2b). We also observed that this is possible with pentamethylcyclopentadienyltris(acetonitrile)ruthenium(II) hexafluorophosphate, **6**. In this case, acetonitrile substitution with styrene oxide gives the CD-active complex **15** without the necessity of using a silver salt which in our opinion renders this sensing protocol increasingly practical (Figure 2c). Additional optimization efforts then showed that the 10-fold excess of **1** is not needed and [Cp*Ru(η^6-styrene oxide)]PF_6, **15**, having very strong ICD amplitudes is in fact formed almost instantaneously and quantitatively with equimolar sensor-substrate amounts using acetone as solvent at room temperature (see below and SI). It is noteworthy that **6** is air-sensitive but the resulting η^6-arene coordination complexes are air-stable at room temperature. This allowed us to grow several single crystal structures and it greatly facilitates the sample handling and CD experiments.

The proposed reaction and binding motif were confirmed by ^{1}H NMR and X-ray analysis and we determined that the same results are obtained with the nonpermethylated $[CpRu]^+$ analog as one would expect. Mixing of stoichiometric amounts of **1** and **6** in deuterated acetone showed complete coordination within one minute (Figure 3). The η^6-coordination is apparent from the large upfield shift of the aromatic styrene oxide proton signals while the epoxide protons undergo relatively small but nevertheless characteristic downfield shifts. Moreover, the molecular recognition with sensor **6** is a smooth and well-defined ligand substitution process that does not show any sign of byproduct formation by NMR analysis. We were able to obtain a single crystal suitable to crystallographic analysis by slow diffusion of pentane into a solution of **15** in chloroform. The crystal structure analysis confirmed the structure of **15** and the η^6-arene binding motif.[51]

Before we continued with screening other chiral substrates we decided to evaluate effects of aryl substituents on the acetonitrile substitution reaction to get a preliminary idea of the expected sensing scope. NMR analysis of the reaction of $[Cp^*Ru(ACN)_3]PF_6$ with various aromatic test compounds including competition experiments showed that the η^6-coordination is irreversible and that electron-rich arenes generally react ten times faster than electron-deficient ones. Nevertheless, the binding of challenging substrates like nitrobenzene is quantitative and complete within 15 minutes (see SI). This encouraged us to examine the general utility of chirality sensing with **1** using a broad selection of chiral target compounds (Figure 4a). We were pleased to observe CD inductions with phenylethylamine, **16**, 1-phenylethanol, **17**, and *N,N*-dimethyl 1-phenylethylamine, **18**, a challenging tertiary amine that cannot be sensed by currently available chiroptical methods that either rely on Schiff base formation, nucleophilic addition or substitution reactions. We then found that our method is also applicable to compounds **19**-**23** carrying amino, alcohol, amide, ester and lactone groups which prompted us to proceed to more complicated structures (see Figure 4a and SI). Chiroptical recognition of the axial chirality in the sterically hindered biphenyl **24** which was obtained in both enantiomeric forms gave strong ICD effects (Figure 4b). Chirality sensing of Hyoscyamine, **25**, Totarol, **26**, Glabridin, **27**, Cryptotanshinone, **28**, 2-((trityloxy)methyl)oxirane, **29**, Podophyllotoxin, **30**, Estradiol, **31**, Estriol, **32**, Ethynylestradiol, **33**, Cephalotaxine, **34**, Zolmitriptan, **35**, Ambrisentan, **36**, Camphothecin, **37**, Levamlodipine, **38**, Nicergoline, **39**, and Reserpine, **40**, is also possible which altogether demonstrates a very broad application scope. In some cases, for example with Nicergoline, the molecular recognition results in very strong ICD amplitudes which would allow chirality sensing at micromolar concentrations (Figure 4b). Importantly, the free chiral compounds are CD-silent in the regions of interest and further testing revealed that the induced CD effects increase linearly with the sample %*ee* which we expected would facilitate quantitative sensing efforts (see below). However, we also observed that the arene-binding sensing method has limitations as some analytes are either inherently CD-active or produce negligible CD effects if any upon coordination to **6** (see SI). We were able to grow single crystals of the Cp*Ru complexes of **16**, **18**, **22**, and **23** for crystallographic analysis which provided additional evidence that η^6-arene coordination is the underlying binding motif of chiroptical sensing with **6** (Figure 4C).

Table 1. Quantitative concentration and *er* sensing with a relay assay. Structures of only one enantiomer for each target compound are shown for clarity. The crystal structures are shown without the hexafluorophospate counteranion.

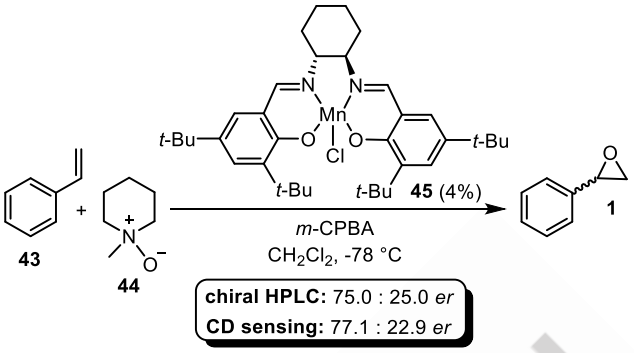


Sample Composition			Sensing Results		
Abs. Config.	Conc. (mM)	Enantiomeric Ratio	Abs. Config.	Conc. (mM)	Enantiomeric Ratio
R	5.0	45.0 : 55.0	*R*	4.9	44.2 : 55.9
R	4.5	2.0 : 98.0	*R*	4.4	4.2 : 95.8
S	4.0	70.0 : 30.0	*S*	3.8	72.5 : 27.5
R	3.5	22.0 : 78.0	*R*	3.4	22.9 : 77.1
S	3.0	60.0 : 40.0	*S*	2.8	61.4 : 38.7
R	2.5	10.0 : 90.0	*R*	2.4	9.3 : 90.7
R	2.0	35.0 : 65.0	*R*	1.8	33.6 : 66.4
S	1.5	75.0 : 25.0	*S*	1.3	78.5 : 21.5
R	1.0	20.0 : 80.0	*R*	0.9	20.7 : 79.3
S	3.0	82.0 : 18.0	*S*	2.8	84.1 : 15.9

Abs. Config. = absolute configuration, Conc. = concentration. The *er* values were determined by CD sensing at 324 nm. The absolute configuration was assigned by comparison of the sign of the ICD signals with a reference. Concentrations were determined by UV analysis at 474 nm. See SI for experimental details.

We then decided to investigate the possibility of quantitative chiroptical sample analysis with our model compound **1**. For this, we developed a relay assay in which nonracemic test samples of styrene oxide at varying total concentration ([*R*]+[*S*]) and different *er*'s ([*R*]/[*S*]) are subjected to excess of the sensor followed by addition of the tridentate ligand **41**. The quantitative formation of the η^6-arene complex and capture of remaining sensor with **41** serving as the relay baton that connects the CD and the UV assay components then gives the stable complex **42** that produces a characteristic UV maximum at 474 nm. The structure of this complex was confirmed by crystallographic analysis and we determined that the intensity of its UV signal is linearly correlated to the amount of unreacted sensor and thus allows calculation of the original concentration of the styrene oxide sample (Table 1). Since the UV responses in our sensing assay originate from the achiral ruthenium complex **42** they are independent of the enantiomeric sample composition and thus allow determination of the total concentration of a chiral compound irrespective of the enantiomeric ratio while the sense and magnitude of the ICD signals obtained from **15** are correlated with the absolute configuration and *er*. The practicality and accuracy of this concept were evaluated with 10 test samples (Table 1). For example, we determined an *er* of 44.2 (*S*) : 55.9 (*R*) and a total concentration of 4.9 mM for a 5.0 mM sample containing 45.0% of the *S*-enantiomer and 55.0% of (*R*)-**1** (entry 1). The UV/CD analysis of a solution of **1** at 1.0 mM with an *S*/*R* ratio of 20.0 : 80.0 gave 0.9 mM and an enantiomeric composition of 20.7 : 79.3 (entry 9). The other results shown in the table confirm that the strategy to decouple concentration and *er* sensing works well without exception. The absolute error margins are very competitive within the optical sensing realm and generally considered acceptable for high-throughput screening applications.[11] To this end, it is important to note that our chromatography-free sensing assay is amenable to widely available automated pipetting instrumentation and multi-well plate UV/CD readers.

To compare our sensing assay to traditional chiral HPLC analysis, we carried out the enantioselective epoxidation of styrene, **43**, following an unoptimized literature protocol with the commercially available manganese complex **45** as catalyst (Scheme 1).[52] The crude reaction product was applied in our relay assay with the piano stool sensor **6** and an enantiomeric ratio of 77.1 (*S*) : 22.9 (*R*) was determined which compares well with the chiral HPLC result (see SI). Importantly, the use of our optical analysis protocol is advantageous due to improved time efficiency, reduced solvent waste production, and compatibility with high-throughput experimentation equipment that can automate parallel screening of hundreds of samples in contrast to the one-sample-at-a-time approach of inherently serial chromatographic methods.



Scheme 1. Comparison of chiral HPLC and CD sensing analysis of an asymmetric styrene epoxidation. *m*-CPBA=*m*-chloroperoxybenzoic acid.

In summary, we have described the first examples of optical sensing of chiral compounds based on click-like η^6-arene coordination to achiral metal complexes. The use of $[Cp^*Ru(CH_3CN)_3]PF_6$ in this unprecedented approach to quantitative chiroptical molecular recognition was found to offer several features that are particularly attractive. First, the sensing concept and target molecule binding with this commercially available Ru(II) piano stool are based on well-defined stoichiometric arene coordination via irreversible acetonitrile displacement which was confirmed by NMR and crystallographic analyses of several complexes. Second, this chemistry does not require excess of the sensing target compound, is complete within a few minutes at room temperature. Importantly, aromatic rings are frequently encountered in chiral compounds, including pharmaceutically relevant multifunctional molecules, and we were able to demonstrate a wide application scope with many examples. Third, a relay assay that decouples the determination of the enantiomeric analyte composition and of the total sample amount with simple CD and UV measurements was developed and successfully tested. Fourth, chromatography-free asymmetric reaction screening is also possible. Finally, the introduction of the [Cp*Ru(II)] piano stool to chiroptical sensing extends the scope of currently known methods that require amine, alcohol, carboxylate or other privileged functional groups and the binding stoichiometry, organic solvent compatibility and red-shifted optical signal inductions of the η^6-arene metal coordination sensing compare favorably with most assays that rely on the formation of inclusion complexes. The demonstration of chiroptical molecular recognition via η^6-arene coordination and its real-world utility have wider implications and are expected to stimulate the development of similar methods or biomolecule labeling techniques. The click-like sensing protocol with piano stool complexes described herein can be readily adapted by any laboratory interested in chiral compound analysis and high-throughput workflows.

Supporting Information

Experimental details, compound characterization data, NMR, UV and CD spectra, and crystallographic details. The authors have cited additional references within the Supporting Information.[53]

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Conflict of Interest

The authors declare no competing financial interest.

Keywords: chirality • piano stool complex • η^6-arene coordination • click chemistry • optical sensing

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[51] Deposition numbers 2313000 (for **15**), 2312999 (for **16**), 2313002 (for **18**), 2312997 (for **22**), 2313998 (for **23**), and 2313001 (for **42**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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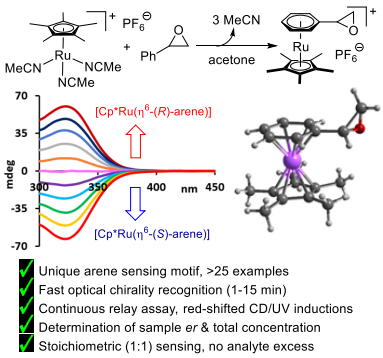
Entry for the Table of Contents



- ✓ Unique arene sensing motif, >25 examples
- ✓ Fast optical chirality recognition (1-15 min)
- ✓ Continuous relay assay, red-shifted CD/UV inductions
- ✓ Determination of sample *er* & total concentration
- ✓ Stoichiometric (1:1) sensing, no analyte excess

Molecular recognition of chiral compounds through click-like η^6-arene coordination with a readily available ruthenium piano stool complex and its use in an optical CD/UV relay assay allow time-efficient chromatography-free stereochemical analysis of a broad range of challenging molecules.

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