COMMUNICATION

Streamlined Asymmetric Reaction Development: A Case Study with Isatins

F. Yushra Thanzeel, Kaluvu Balaraman and Christian Wolf

Abstract: Asymmetric reaction development within a day or two has been a dream of synthetic chemists for several decades. We now show that such a task is feasible with a highly efficient streamlined screening strategy using the asymmetric allylation of isatins with a chiral boron complex as a case study. Our high-throughput screening (HTS) method is based on fast optical UV/CD analysis of minute amounts of crude reaction mixtures (~ 3mg scale) and it obviates product isolation and the general need for reference compounds which greatly reduces preliminary work and analysis time. The setup, reaction screening, analysis and data processing for 54 asymmetric allylations of 9 different isatins in 6 different solvents was handled by a single operator in less than 20 work hours. One could easily extend this HTS strategy to hundreds of reactions in roughly the same time frame and further reduce the labor with commercially available automated high-throughput experimentation equipment. The effectiveness of this asymmetric reaction development strategy is confirmed with the upscale synthesis of two representative 3-allyl-3-hydroxyisatins in 98-99% yield and with 91-94% *ee* under optimized conditions.

Asymmetric reaction development is a central task in the chemical and pharmaceutical sciences. Despite impressive advances with high-throughput equipment, the optimization of the yield and the enantiomeric excess of a chiral product often remains a major bottleneck that limits the overall progress and the workflow, especially in highly collaborative settings where on-time delivery of drug candidates for preclinical studies is critical. Such a scenario may arise, for example, at the early drug discovery stage where it is necessary to quickly select and establish a synthetic method that affords fast and reliable access to an urgently needed compound and analogues thereof for initial testing purposes. Expectations of short response times to urgent compound requests generate operational constraints that can make this a daunting challenge. As the major focus typically lies on time-efficiency and expeditious production of the target compound(s) the use of catalysts or reagents that are not commercially available and have to be prepared separately may not be acceptable. At the same time, analytical tools that allow determination of the conversion or yield when a large number of miniaturized reactions are performed in parallel to identify optimal conditions must be in place and ready for use. With the help of high-throughput screening techniques and automated equipment that have become routine in many laboratories, the development of a satisfactory synthetic route can often be accomplished fairly quickly when the goal is to prepare achiral compounds.[1]

This may not be the case, however, when a chiral product in high yield and enantiomeric excess (*ee*) is needed. The determination of either conversion or yield and *ee* values often involves two separate methods and elaborate purification steps prior to the analysis. The common use of chiral chromatography for *ee* determination introduces several problems. First, it generally requires time-consuming screening of several chiral columns and mobile phase compositions to achieve baseline enantioseparation unless a literature protocol exists. Second, it typically necessitates the synthesis and isolation of racemic reference materials for this task. Third, the separation of enantiomers by HPLC and GC methods may take several minutes to an hour which makes the analysis of many reaction samples tedious and inefficient.[2] Unfortunately, some of these issues remain when NMR chiral solvating agents are used.[3] Alternatively, mass spectrometric[4] and optical methods[5] that are compatible with parallel screening of small-scale reactions conducted in multi-well plates offer increased analysis speed and high throughput. Carefully designed optical sensors have been successfully applied in asymmetric reaction screening trials in recent years, a prime example is a CD/TLC hybrid approach by Krische and Anslyn.[6] The implementation of these assays, however, involved extensive preparative efforts and the use of enantioenriched reference compounds, e.g. for the production of calibration curves, which still creates an operational hurdle and slowdown. We now wish to report a practical strategy that greatly accelerates asymmetric reaction developments even when parallel screening with several substrates is desired. We show that initial optimization and testing of a chiroptical sensing protocol can be reduced to a minimum which eliminates a common bottleneck in many academic and industrial laboratories and allows one to directly proceed with the reaction screening. A task that typically takes weeks to several months can thus be accomplished in a few days or even within a 24 hour period.

At the onset of this study, we decided to select the asymmetric allylation of isatins as a test reaction. The introduction of an allyl group at C-3 in the isatin scaffold affords chiral 3-hydroxyoxindoles which are important precursors for the synthesis of biologically active compounds.[7] From our experience with isatin transformations we were aware that asymmetric nucleophilic addition reactions give oxindoles exhibiting diminished UV absorption and strong circular dichroism (CD) signals.[8] We reasoned that these spectroscopic changes can be easily measured using a small reaction aliquot to evaluate the conversion and degree of asymmetric induction, respectively, without the need to isolate the product. During our search for a new asymmetric allylation procedure under the operational

[a] F. Y. Thanzeel, K. Balaraman, C. Wolf
Department of Chemistry
Georgetown University
37th and O Streets, Washington, DC 20057 (USA)
E-mail: cw27@georgetown.edu

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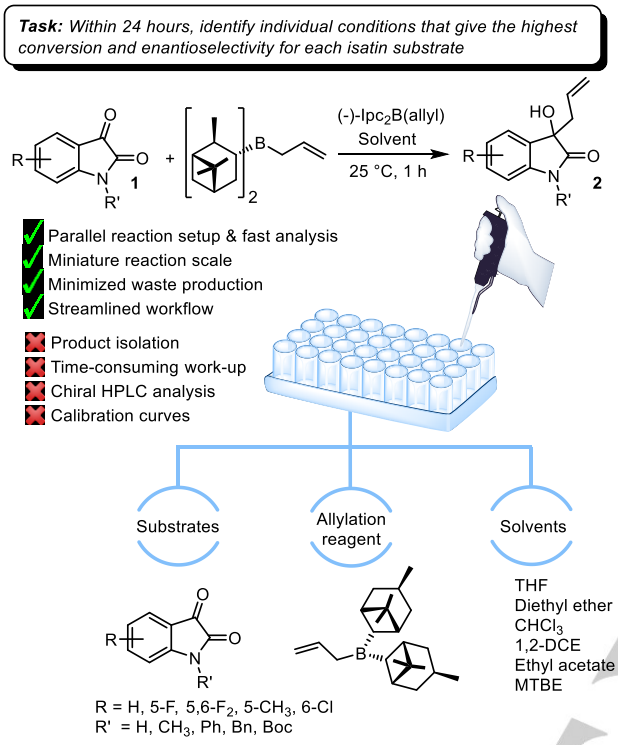
restrictions discussed above, i.e. exclusion of any reagents or catalysts that would have to be synthesized, we were surprised to find that the widely successful and commercially available Ipc_2(allyl)borane complex had not been applied to isatins.[9]



Scheme 1. Reaction development task.

We selected nine isatin compounds and six different solvents (THF, diethyl ether, chloroform, 1,2-dichloroethane, ethyl acetate and *tert*-butyl methyl ether) to test the possibility of accelerated asymmetric reaction screening. The parameters and boundaries of the isatin allylation development task are summarized in Scheme 1. Our high-throughput optimization strategy has several attractive features. It is amenable to commercially available high-throughput screening and automated chiroptical sensing equipment, it relies on small-scale reactions to minimize cost and waste production, it eliminates time-consuming work-up procedures and product isolation, and it replaces chromatographic *ee* analysis with fast optical measurements. Finally, our screening approach is ready for use after very little preliminary work because it obviates the common need for isolated (non)racemic reference compounds which are typically prepared prior to the beginning of the actual reaction optimization and used to develop an analytical method for *ee* determination.

The preliminary work needed in preparation of the chiroptical analysis of the asymmetric allylation of isatins **1a-i** is generally straightforward and not time-consuming. First, a test reaction in a small vial was conducted with isatin **1b** which was selected as a representative example. Quenching of the reaction with $NaOH/H_2O_2$ followed by addition of HCl produces homogeneous reaction mixtures with stable chiroptical signals.[6c] We then collected the UV spectrum of **1b** and the UV and CD spectra of the quenched crude reaction mixture containing the corresponding allylic alcohol **2b**. These fast optical measurements revealed the CD and UV windows that can be exploited to determine the conversion and the degree of the asymmetric induction which is indicative of the *ee* of the allylation product (Figure 1). It is noteworthy that the allylation coincides with the disappearance of the characteristic red color of the isatins which serves as a good indication of the reaction progress. Accordingly, the isatin UV absorption at approximately 420 nm disappears as it is converted to the allyl alcohol and a CD signal around 265 nm appears when nonracemic product is formed. The purpose of these experiments was to develop a protocol for quenching of the allylation reaction and to establish the optimal concentration for simultaneous UV and CD analysis from a small aliquot of the reaction mixture. Importantly, isolation of the product is not necessary because neither a reference standard nor a calibration curve is required for our screening assay.

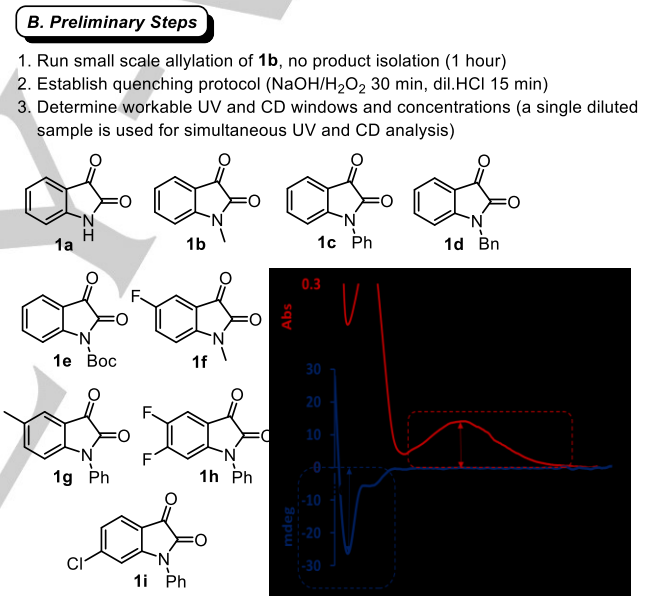


Figure 1. Preliminary experiments and selected isatins **1a-i**.

With a high-throughput screening (HTS) protocol in hand, we were able to set up the parallel reaction screening assay. As mentioned above, we selected the 9 representative isatin compounds **1a-i** and 6 solvents to determine the preferred conditions for the asymmetric allylation with Ipc_2(allyl)borane complex. The setup of the corresponding 54 reactions and the workflow with the individual time periods required to accomplish all the individual tasks manually by a single operator are shown in Figure 2. First, stock solutions of the substrates in THF were prepared and 100 µL aliquots were transferred into small vials. The solvent was then removed and the vials were transferred into a drybox. The individual reactions were then started by adding 1 mL of the reaction solvent and the borane reagent. After 1 hour, the reactions were quenched with basic hydrogen peroxide, acidified with HCl and a small aliquot was diluted with either

chloroform or methanol for direct UV/CD analysis (see SI for details). All steps were completed within 12.5 hours. Alternatively, the operations could have been conducted with significantly less labor and probably in a shorter timeframe if commercially available automated sample handling and analysis instrumentation had been used. For example, the solution preparation and CD/UV measurements can in principle be achieved on a microwell plate format with a pipetting robot and a fully automated Ekko UV/CD reader. One can easily imagine that the HTS operation can be extended to hundreds of asymmetric reactions if it is desirable to include variation of more reaction parameters.

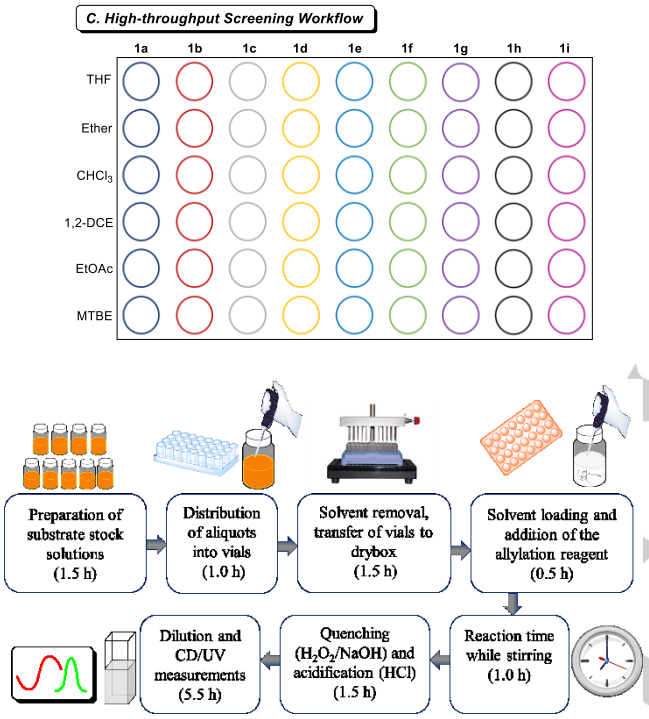


Figure 2. HTS setup and workflow. The reactions were conducted using approximately 3 mg of the isatins (12.5 mM, 1 mL of solvent) and the chiroptical analyses were performed using 15-20 µL aliquots of the reaction mixtures and dilution to 94-125 µM with chloroform or methanol.

With the goal to identify the best solvent for the asymmetric allylation of each substrate we then processed the chiroptical data using the CD and UV windows shown in Figure 1. The decline of the UV absorption signal allowed us to quantify the conversion of the isatin to the allylic alcohol derivative. Because we have deliberately eliminated the prerequisite of reference compounds and time-consuming chiral HPLC analysis of each run, we do not determine exact *ee* values here. However, the induced CD signal increases proportionally with the enantioselectivity of the reaction. For quantification purposes, we introduce the term normalized asymmetric induction (NAI) which considers the measured CD intensity and the relative amount of product formed which is available from the conversion (Equation 1). The use of the UV change for the determination of the conversion and the NAI as conversion-independent enantioselectivity parameter allows to differentiate between conditions that give, for example, 90% conversion and 10% *ee* from conditions that result in 10% conversion but with 90% *ee*. To further corroborate this concept, we confirmed with a few representative reactions that the NAI values correctly reveal the solvent effects on the product *ee* by chiral HPLC analysis (SI).

Equation 1 $$NAI = \left[\left(\frac{CD\ in\ mdeg}{Conversion} \right) * 100 \right]$$

The processing of all data was accomplished in less than 2 hours and the results of the chiroptical analysis of each allylation reaction are shown in Figure 3 (see SI for details). We observed high conversion of the unprotected isatin, **1a**, ranging from 89 to 93% after 1 hour with all solvents but clearly the highest NAI values of 84-85 mdeg were measured for diethyl ether and ethyl acetate. The other solvents gave NAI's of only 78 mdeg (THF) or 59-68 mdeg (chloroform, dichloroethane and *tert*-butyl methyl ether). The conversion of **1b** to **2b** exceeded 90% in all trials but diethyl ether is the solvent of choice as it produces the highest asymmetric induction (NAI = 86 mdeg). Similar trends were determined for the reactions with **1c** and **d**. The preferred solvents for the allylation of the *N*-boc protected isatin **1e** are THF and ethyl acetate whereas MTBE is clearly superior in the case of *N*-methyl-5-fluoroisatin, **1f**. The transformation of **1g** to **2g** can be expected to be most successful in either chloroform or ethyl acetate while very similar conversion and NAI values were obtained for **1h** with all solvents except MTBE which apparently is highly detrimental to the enantioselectivity. Finally, **2i** was produced with the highest NAI (61 mdeg) and 80% conversion when ethyl acetate was used as solvent. Comparison of the results obtained with the differently substituted *N*-methylisatins **1b** and **f** or for the series of *N*-phenylisatins **1c**,**g**,**h** and **i** reveals that solvent optimization is important to determine optimal reaction conditions for each substrate as substituent effects play an important role.[10] We note that in many cases asymmetric reactions produce chiral compounds that do not carry a chromophore and are devoid of quantifiable UV and CD signatures. Although we have selected an asymmetric reaction that coincides with a decrease of the characteristic UV band of isatins and yields an intrinsically CD active product, we emphasize that our HTS strategy can also be adapted to reactions with UV/CD-silent compounds. For such applications, we and others have shown that quantification of product formation and *ee* values can be achieved by using chiroptical sensors that generate distinct UV and CD signals.[5,6,11]

In this study, we considered a request frequently encountered by synthetic chemists working in a collaborative, interdisciplinary environment which is to quickly develop an efficient process that affords chiral compounds selected for pharmaceutical studies or other testing purposes. The task, therefore, is to rapidly identify substrate-specific reaction conditions that allow the synthesis of one or several chiral compounds in optimal yield and enantiomeric excess using readily available starting materials and HTS tools. To demonstrate how such expectations can be met with our streamlined HTS approach we decided to run two representative allylations on a 50 mg scale. In preparation of this final task we ran the allylation of **1d** under the optimized conditions in diethyl ether for 1 hour using 3 mg of the isatin at room temperature. This

gave **2d** in 80% ee according to chiral HPLC analysis. We concluded that it would be advantageous to perform the 50 mg reactions under cryogenic conditions with the hope to maximize the enantioselectivity. Having determined that diethyl ether and

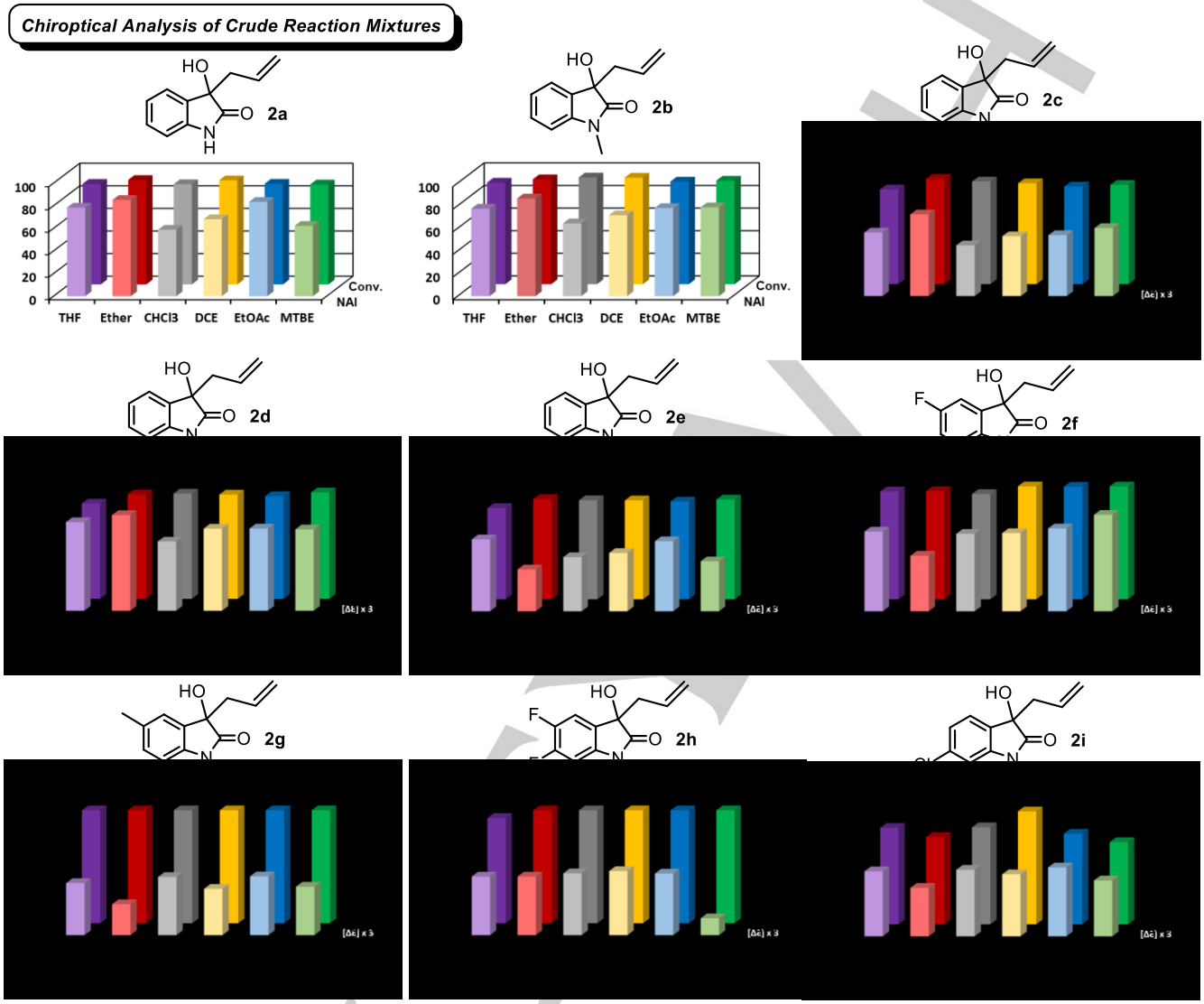
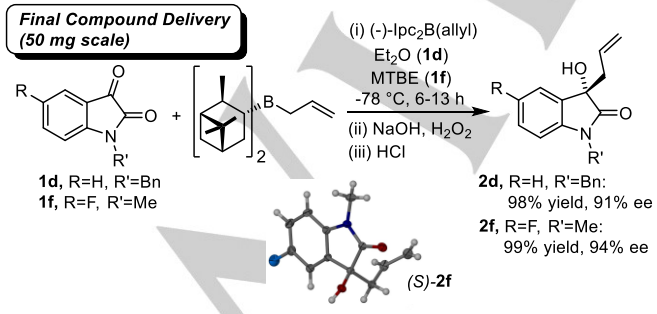


Figure 3. HTS results. Conv. = Conversion based on UV analysis. NAI = Normalized asymmetric induction based on the intensity of the CD signal measured in mdeg (NAI = [mdeg] • 3/Conv.). The factor 3 was applied for visualization purposes.



Scheme 2. Exemplary upscaling of the asymmetric allylation using the best HTS hits obtained with **1d** and **1f** at -78 °C.

MTBE are the solvents of choice for the asymmetric allylation of **1d** and **1f**, respectively, we therefore performed the two reactions with (-)-Ipc$_2$B(allyl) at -78 °C (Scheme 2). We were very pleased to find that the corresponding allylic alcohols **2d** and **2f**, were obtained in 98-99% yield and with 91-94% *ee* which was verified by chiral HPLC (SI).[12]

In summary, we have introduced a high-throughput screening strategy that streamlines asymmetric reaction development using the allylation of isatins with a chiral boron complex as a case study. The search for synthetic methods that produce chiral compounds in high yield and enantiomeric excess and the determination of individual conditions that give optimal results with different substrates, for example various isatin derivatives, is often very time-consuming, tedious and can take

several months. We now show that these tasks can be accomplished in a few days. Our HTS method is based on fast optical analysis of minute amounts of crude reaction mixtures and it is amenable to automated high-throughput experimentation equipment. It obviates product isolation and the general need for reference compounds that are traditionally used to develop either NMR and chiral HPLC methods or calibration curves for optical assays. A minimum of preliminary work is required to identify suitable sample concentrations and other parameters for the parallel reaction setup and the UV/CD analysis. The reaction screening can therefore be started without much delay. While we screened 54 asymmetric allylations of 9 different isatins in 6 different solvents one could easily extend this HTS strategy to investigate hundreds of reactions in the same time frame. This study revealed ideal conditions for each isatin derivative which demonstrates that one can very quickly establish an individually optimized substrate scope. Such a task is very time-consuming but necessary in frequently observed cases where a single synthetic protocol does not work equally well with differently substituted starting materials. The effectiveness of our asymmetric reaction development strategy was confirmed with the upscale synthesis of two representative 3-allyl-3-hydroxyisatins in 98-99% yield and with 91-94% *ee*. Finally, we note that our strategy eliminates cumbersome *ee* analysis from the HTS stage, the enantiopurity of the chiral compounds obtained at the production stage under optimized conditions still has to be determined, for example by a chiral HPLC run, of course.

Acknowledgements

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Keywords: High throughput screening • Asymmetric reaction development• Circular dichroism • UV spectroscopy • Isatins

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[12] During the preparation of this manuscript we obtained single crystals for **2b** and **2f** which showed formation of the (*S*)-enantiomer as the major product (SI). The CCDC numbers for the compounds are 1903956 (**2b**) and 1903957 (**2f**). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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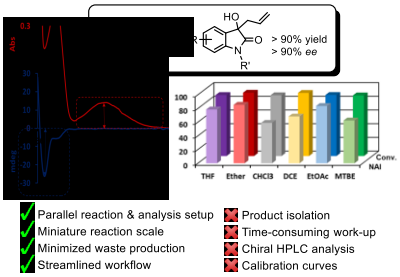
A new approach that accelerates asymmetric reaction screening without the need for individual calibration curves is presented using the allylation of isatins as an example.



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