



*Citation for published version:*

Greenhalgh, MD, Taylor, JE & Smith, AD 2018, 'Best practice considerations for using the selectivity factor,  $s$ , as a metric for the efficiency of kinetic resolutions', *Tetrahedron*, vol. 74, no. 38, pp. 5554-5560.  
<https://doi.org/10.1016/j.tet.2018.05.069>

*DOI:*

[10.1016/j.tet.2018.05.069](https://doi.org/10.1016/j.tet.2018.05.069)

*Publication date:*

2018

*Document Version*

Peer reviewed version

[Link to publication](#)

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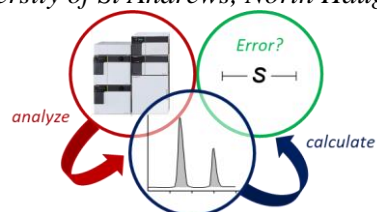
## Graphical Abstract

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### Best practice considerations for using the selectivity factor, $s$ , as a metric for the efficiency of kinetic resolutions

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# Best practice considerations for using the selectivity factor, $s$ , as a metric for the efficiency of kinetic resolutions

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## ARTICLE INFO

### Article history:

Received  
Received in revised form  
Accepted  
Available online

### Keywords:

Kinetic resolution  
Selectivity factor  
Data analysis  
Error calculations  
HPLC analysis

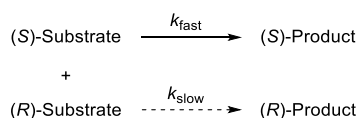
## ABSTRACT

The suitability of using the selectivity factor,  $s$ , as a reaction metric for kinetic resolution reactions and the errors associated with its measurement are considered. Investigation of the analytical error associated with HPLC analysis of a kinetic resolution reveals that one of the largest potential sources of variation arises from the ability of a practitioner to integrate the peaks from a single analysis. The consequences of this error on the reliability of reported  $s$  values are discussed, and some general rules for good practice regarding the use and reporting of  $s$  as a metric are suggested.

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## 1. Introduction

Kinetic resolution (KR) is a widely-used process in academia and industry for separating the enantiomers of a substrate from a racemic or scalemic mixture (Scheme 1).<sup>1</sup> The principle of KR relies on the reaction of a chiral reagent or chiral catalyst-derived species with each enantiomer of the substrate taking place *via* diastereomeric transition states. The difference in free energy between these two transition states ( $\Delta\Delta G^\ddagger$ ) dictates the difference in rate constants ( $k$ ) for the reaction of each enantiomer. Effective KR protocols have been developed for numerous substrate classes using many different types of reaction including acylation, oxidation, silylation, nucleophilic ring-opening, and cycloadditions amongst others.<sup>1</sup>



**Scheme 1.** General KR reaction.

The most commonly-applied metric to assess the efficiency of a given KR is the selectivity factor ( $s$ ), which is defined as the rate constant for the reaction of the fast-reacting enantiomer divided by the rate constant for the slow-reacting enantiomer (eq. 1). Consequentially,  $s$  can also be related to the difference in free energy between the diastereomeric transition states ( $\Delta\Delta G^\ddagger$ ).

$$s = \frac{k_{\text{fast}}}{k_{\text{slow}}} = e^{\Delta\Delta G^\ddagger/RT} \quad (1)$$

While the direct measurement of such kinetic parameters is practically challenging,  $s$  is usually more conveniently calculated using the reaction conversion ( $c$ ) and the % enantiomeric excess ( $ee$ ) of either the recovered substrate or the reaction product (eq. 2 or eq. 3, respectively) as originally outlined by Sih and co-workers<sup>2a</sup> for enzymatic KRs, and Kagan and Fiaud<sup>2b</sup> for general cases.<sup>3</sup> The reaction conversion ( $c$ ) can itself be conveniently calculated using the  $ee$  of recovered substrate and product (eq. 4). Importantly, calculation of  $s$  using these equations requires the KR to be irreversible and first-order in substrate for the selectivity-determining step, with more detailed kinetic analysis required to interrogate processes with more complex rate laws.<sup>4,5</sup>

$$s = \frac{\ln[(1-c)(1-ee_{\text{substrate}})]}{\ln[(1-c)(1+ee_{\text{substrate}})]} \quad (2) \quad s = \frac{\ln[1-c(1+ee_{\text{product}})]}{\ln[1-c(1-ee_{\text{product}})]} \quad (3)$$

$$c = \frac{ee_{\text{substrate}}}{ee_{\text{substrate}} + ee_{\text{product}}} \quad (4)$$

The distinct rate constants for the reaction of each enantiomer of substrate mean that the relative concentrations, and hence relative *rates* of reaction, of each enantiomer vary throughout the course of a KR. The non-linear relationship between conversion and  $ee$  in a KR makes comparison of two different reactions using only these parameters difficult. Therefore  $s$ , if used correctly, is a particularly useful metric for comparing different

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KRs, as for a given process  $s$  should remain constant and be independent of the reaction conversion.<sup>6</sup> However, the logarithmic nature of  $s$  makes direct comparison of values for different KRs non-intuitive. For example, while the difference in synthetic utility for two reactions that give yields of 50% and 90% is readily understood, the same is not the case for KRs with  $s = 50$  and 90. Moreover, the non-linear nature of the equations used to calculate  $s$  means that small inaccuracies in measuring either conversion or ee can lead to large variations in  $s$ . It is commonly appreciated that an enantioselective reaction reported as giving 99% ee and 70% yield will have small errors associated with measuring these values;<sup>7</sup> however the magnitude of error in  $s$  calculated for a KR measured to give 99% ee at, for example, 52% conversion is not as easily inferred. To exemplify this point, uncertainty in the measurement of ee within the range 98.5–99.5% ee for a KR at 52% conversion results in variation in the calculated value of  $s$  in the range of 102–138; while the same uncertainty in ee for a KR at 55% conversion results in a smaller spread of  $s$  values in the range of 44–57.

A convenient visual comparison of reactions with different  $s$  values is obtained by plotting conversion against either substrate or product ee (Figures 1 and 2). For each value of  $s$ , the ee of substrate increases throughout the reaction (Figure 1), while the ee of product starts at a maximum value and decreases, tending towards 0 at 100% conversion (Figure 2). The initial maximum ee of product is inherently limited by  $s$  (eq. 1). For example, in a KR with  $s = 10$ , the maximum ee of product is determined by the ratio of rate constants for the reaction of each enantiomer, leading to an initial ee of ~82% (91:9 er). In contrast, the ee of substrate continues to increase over the full reaction course, allowing the isolation of highly enantioenriched material even for KRs with only a modest  $s$ . For example, in a KR with  $s = 10$ , the unreacted substrate can be recovered at 72% conversion (maximum 28% yield) in 99% ee. Such plots also highlight the errors associated in calculating  $s$ ,<sup>4,5</sup> with only small inaccuracies in measuring either conversion or ee leading to potentially large difference in the calculated value of  $s$ , a problem that is expected to be particularly exacerbated for high  $s$  values.

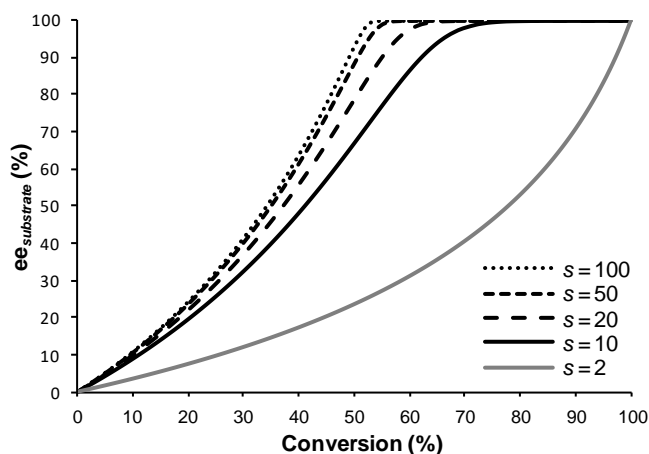


Figure 1. Evolution of %ee of substrate with reaction conversion.

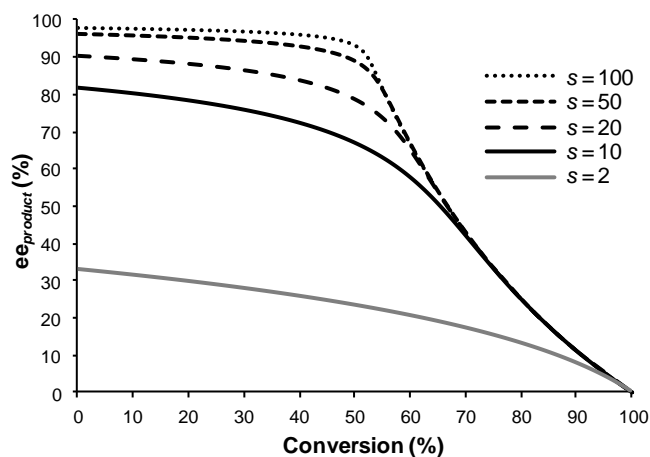


Figure 2. Evolution of %ee of product with reaction conversion.

The power of modern catalytic methods has led to numerous advances in kinetic resolutions to provide a range of highly effective resolution processes. However, based upon our experience from a practical perspective, as well as informative referee comments, the use of  $s$  as a metric for kinetic resolutions is often misrepresented. In particular, the suitability and accuracy of reporting  $s$  values often does not take errors into consideration, particularly for values of  $s > 50$ . Herein, we first outline suggested experiments and analyses to ensure that  $s$  is an appropriate metric for a given KR. From a practical perspective we propose a simple approach to estimating the analytical and operational error in measuring conversion and ee, and highlight the implications these have on the calculation of  $s$ . Considering these errors in the context of synthetic applicability, suggested boundaries for reporting  $s$  values to an appropriate number of significant figures are put forward. These general guidelines should aid in the comparison and use of  $s$  to evaluate the effectiveness of a KR.

## 2. Results and Discussion

### 2.1 Nomenclature

There is currently no universally accepted abbreviation for “selectivity factor” in KRs, with  $s$  (italics),  $S$ ,  $s$  (bold) and  $k_{rel}$  all having been used in the literature, while the abbreviation  $E$  is commonly used for enzymatic KRs. We favour the abbreviation  $s$  (lowercase, italics), as it is most commonly used, is clear in all typefaces, and importantly avoids ambiguity with the main text and/or stereochemical descriptors. For clarity in schemes, and axis and column titles the use of  $s$  (lowercase, italics, and bold) may also be appropriate on the grounds of stylistic discretion.

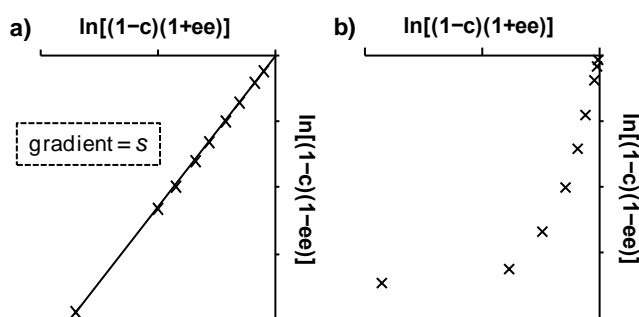
### 2.2 Practical considerations

In a typical small-scale KR performed as part of a method development, or for assessing substrate scope, it is likely that both the experiment and analysis will be performed only once.<sup>6,7</sup> It is therefore important to consider the potential analytical errors associated with the reaction analysis and how this will translate to the calculated  $s$  for the KR. Analytical techniques such as HPLC and GC using a chiral support are most commonly used to determine both substrate and product ee, allowing the reaction conversion ( $c$ ) to be calculated using equation 4. It is important to corroborate these calculated conversions using a second technique, such as NMR spectroscopy, as this approach will quickly identify any major discrepancies that require further investigation (see the following section). Alternative techniques to determine ee,<sup>8</sup> such as NMR<sup>8c-e</sup> or optical methods,<sup>8f-i</sup> may also be appropriate for given substrates. Errors associated with measurements made by HPLC using a chiral support are discussed below, but we anticipate that errors arising from the

use of alternative techniques may be readily estimated in a similar fashion.

### 2.3 Appropriate use of $s$

When studying a KR, the first important consideration is whether  $s$  is an appropriate metric to describe the efficiency of the process. Equations 2 and 3 are only applicable for KRs in which the selectivity-determining step is first order in substrate. While this could be assessed by a detailed kinetic analysis, a more straightforward method is to calculate  $s$  at different conversions as, if applicable,  $s$  should be independent of conversion. Practically, this analysis is best performed by removing aliquots from a single reaction and analyzing each sample by HPLC or GC analysis using a chiral support. This approach minimizes operational errors introduced by performing multiple reactions to different conversions. Important caveats are that each aliquot must be appropriately ‘quenched’ to halt progress of the KR, and the sample must be sufficiently free of impurities to allow reliable analysis. The results are then best processed using a graphical linear regression analysis. For example, plotting  $\ln[(1-c)(1-ee_{\text{substrate}})]$  versus  $\ln[(1-c)(1+ee_{\text{substrate}})]$  (from equation 2) should give a straight line that passes through the origin with the gradient equal to  $s$  (Figure 3a). The  $R^2$  value for the line of best fit allows analytic quantification of  $s$  uniformity over the course of the KR. If a straight line is not obtained from this analysis (for example Figure 3b) it can be concluded that equations 2 and 3 are not applicable, and further investigations are required. One scenario that invalidates the use of equations 2 and 3 is if either the substrate or product racemizes under the reaction conditions, potentially leading to a dynamic kinetic resolution. This possibility can be investigated by applying enantiomerically-enriched substrate or product under the reaction conditions and assessing any changes in enantiopurity. Alternatively, the KR may obey a more complex rate law.<sup>4,5,9</sup> Examples include when the KR is reversible;<sup>9a,b</sup> has a non-first order dependence on substrate; involves sequential enantioselective transformations; exhibits significantly different binding strengths between each enantiomer of the substrate and catalyst;<sup>4g</sup> or if the reaction product interacts with the catalyst to modify its activity. To delineate these possible scenarios in-depth kinetic analysis of the process is required.



**Figure 3.** Linear regression analysis to determine  $s$ : **a)** a KR for which eq. 2 is applicable; **b)** a KR for which eq. 2 is not applicable.

### 2.4 Analytical error in $s$

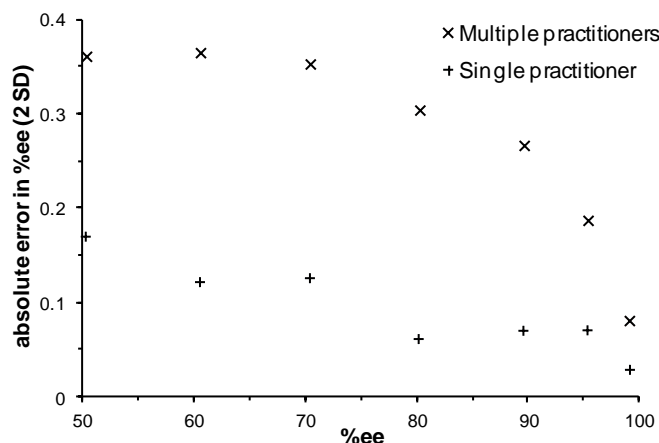
Various approaches have been adopted in the literature to acknowledge the potential errors in  $s$ , including values being reported to a set number of significant figures and/or adopting arbitrary upper-bounds of accuracy (e.g.  $s > 50$ ). Other approaches include repeating the KR multiple times and taking an average, however this only provides information about experimental reproducibility and does not account for potential errors in analysis. In many cases this issue is simply overlooked

which, coupled with the non-intuitive logarithmic nature of  $s$ , makes comparison of values for non-expert readers more difficult.

The error associated with  $s$  can be split into two broad classes: i) analytical error; and ii) operational error. We define the former as the error associated with recording experimental data for a single result,<sup>10</sup> and how that error manifests itself as an error in  $s$ . Operational error is concerned with experimental reproducibility and is discussed in the next section.

In a KR in which both the substrate and product are chiral, the reaction conversion can be calculated from the associated ee values (equation 4), and therefore the overall error in  $s$  is determined by the accuracy of the ee measurements. Such analysis is commonly performed using HPLC or GC with a chiral support, however it is not common practice, particularly in academic laboratories, to either repeat analyses or use calibration curves.<sup>7</sup> This often means that reported results are obtained from a single measurement. To estimate the maximum error in  $s$  obtained from such a single analysis in our laboratory, the precision of our HPLC instrument was determined through a three-peak repeatability test (six runs) using an analytical standard mixture. The average standard deviation in peak area was only 0.10%, showing a high level of reproducibility in the instrument itself.<sup>11</sup> This variation, if applied uniformly to all peaks analyzed, results in only minor errors in ee measurement (e.g.  $50\% \pm 0.15$  ee), which decrease as the ee value increases (e.g.  $95\% \pm 0.02$  ee). However, it should be noted that the reproducibility test itself does not explicitly consider measuring ratios, especially when one is much greater than the other (i.e. high ee), which has previously been reported to be less accurate in single analyses.<sup>7</sup>

A second potentially larger source of error that is not normally considered is the ability of the practitioner to accurately and reproducibly measure ee values, which is typically performed using the analysis software’s manual integration tool (often using HPLC or GC). We suspected that the magnitude of this error would be affected by the ee value being measured, with greater variation more likely for samples of moderate ee. To investigate this hypothesis, seven samples of a chiral alcohol, 1-benzyl-3-hydroxy-3-phenylindolin-2-one, were prepared as scalemic mixtures of 50–99% ee. The error associated with the practitioner’s ability to reliably integrate each HPLC spectra was used to assess the error in the ee value. A single practitioner analyzed each spectra ten times and the mean and standard deviation of the data calculated.<sup>11</sup> The absolute error in the mean value of ee was taken as two standard deviations (Figure 4 +). All errors calculated were quite low ( $< \pm 0.2$  ee) and are comparable with the inherent error associated with the reproducibility of the HPLC itself. As expected, the error in ee decreased with increasing magnitude of ee. However, this initial analysis only assesses the ability of a single practitioner to be self-consistent when integrating the same spectra, and does not necessarily give an idea of the expected variation in the single analysis of different spectra. A more thorough approach was therefore adopted, with the same seven spectra analyzed independently by 20 different practitioners (Figure 4 ×). In this case, a much larger spread of data was obtained, with errors ranging from  $\pm 0.4$  to  $< \pm 0.1$  ee at 99% ee.<sup>11</sup> To simplify the use of this data in further analyses, we assigned representative absolute errors in ee measurement to different ranges of ee values (Table 1).



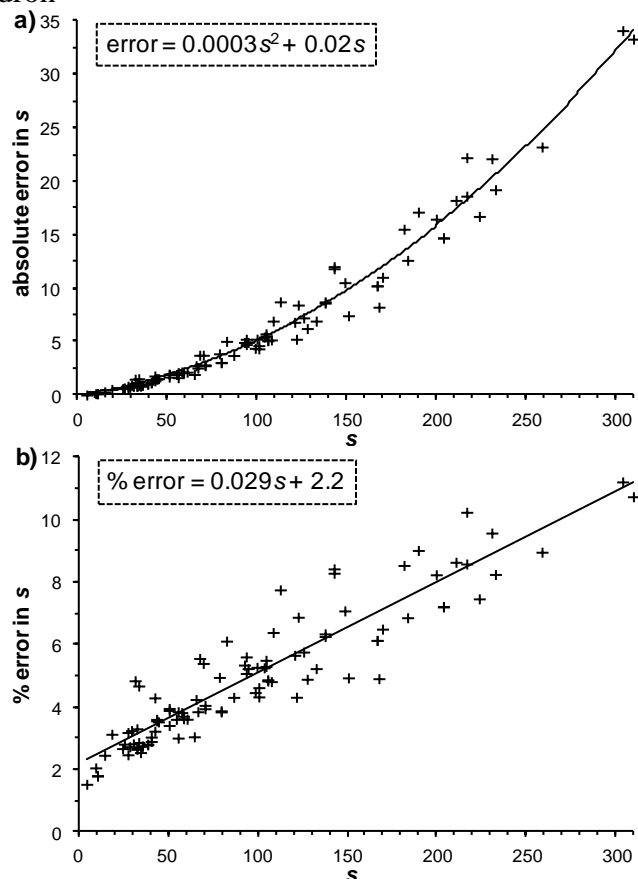
**Figure 4.** Calculated analytical error in %ee values measured using HPLC analysis. + Each data point obtained from 10 analyses by a single practitioner; x Each data point obtained from 14 analyses by 14 different practitioners.

**Table 1.** Error in ee measurement according to the value of ee (based on Figure 4).

ee	absolute error
< 80%	0.4
80–90%	0.3
90–99%	0.2
> 99%	0.08

This analysis also more generally provides an indication of the error involved in the measurement of ee values for any enantioenriched compound. The errors calculated suggest that reporting ee values to the closest integer is appropriate, at least in the range assessed here (50–99% ee). It is important to note that the HPLC samples used for this analysis displayed good signal-to-noise ratio and baseline separation between the peaks of interest. It is good practice to ensure these requirements are satisfied; otherwise the error associated with the measurement of ee will be significantly increased.

Next, an assessment of how these errors in ee translate to error in  $s$  was conducted. This analysis was approached by applying the errors defined in Table 1 to experimentally-determined ee values obtained by HPLC analysis of recovered substrates and products in 100 KR experiments performed in our group on the acylative KR of tertiary alcohols ( $s = 5\text{--}310$ ).<sup>11,12</sup> The largest difference in the calculated value of  $s$  is obtained when the maximum ee values for both recovered substrate and product are used (i.e. recorded value + error). This analysis most likely overestimates the error in  $s$  as it effectively compounds the errors in measuring both substrate and product ee values. Plotting this maximum absolute error in  $s$  as a function of  $s$  suggests that the error increases according to a quadratic polynomial function (Figure 5a, eq. 5). Alternatively, by plotting the % error in  $s$  as a function of  $s$ , a proportional relationship is obtained (Figure 5b, eq. 6). These equations have been used to calculate representative errors associated with a range of selected  $s$  values between 10 and 1000 (Table 2). This analysis demonstrates that errors associated with low  $s$  values are relatively small, while errors in higher  $s$  values are much more significant. This trend could be predicted by a practitioner working in the field; however this analysis provides a simple approach to assess the magnitude of the error likely to be associated with  $s$ .



**Figure 5.** Error in  $s$  as a function of  $s$ : a) absolute error; b) % error.

$$\text{absolute error} \approx 0.0003s^2 + 0.02s \quad (5)$$

$$\% \text{ error} \approx 0.03s + 2 \quad (6)$$

It should be noted that these estimations have been made based upon the error bands for different ee measurements (Table 1) determined by HPLC analysis using a chiral support and standard processing software. The fact that the associated errors in  $s$  are likely overestimated means that this analysis serves as a reasonable guide for other KR experiments analyzed using HPLC. While the same trends in error would be expected for different methods of analysis, the absolute values will be different and should therefore be assessed independently.<sup>13</sup>

**Table 2.** Examples of absolute and % errors in representative values of  $s$ .

$s$	absolute error <sup>a</sup>	% error <sup>b</sup>
10	0.23	2.3
20	0.52	2.6
30	0.87	2.9
40	1.3	3.2
50	1.8	3.5
75	3.2	4.3
100	5.0	5
200	16	8
500	85	17
1000	320	32

<sup>a</sup> Calculated using equation 5. Values given to 2 significant figures.

<sup>b</sup> Calculated using equation 6.

From inspection of Figures 5a and 5b, it is clear that there is reasonable variation within our data for the error associated with each  $s$  value. It was hypothesized that this variation may be related to differences in reaction conversion between each KR experiment. To investigate the effect of reaction conversion on error in  $s$ , simulated data was produced over a range of reaction conversions for KR experiments with  $s = 10, 50$  and  $100$  and the errors

estimated for different reactant and product ee using Table 1 (Figure 6).<sup>11</sup> Following the approach described above to estimate the error in  $s$  reveals that the lowest error in  $s$  is obtained when the KR is analyzed at close to 50% conversion, with significantly larger errors obtained either side of this value. This is particularly significant for KR with very high  $s$ . For example, for a KR with  $s = 50$ , conversions of  $< 55\%$  should be targeted to minimize errors, while for a KR with  $s = 100$ , a conversion in the range of  $\sim 40\text{--}52\%$  is preferable.

For reactions with high selectivity ( $s > 100$ ) where greater accuracy in  $s$  is required, a linear regression analysis (Figure 3) can also be performed.<sup>14</sup> This analysis will provide a value for  $s$  based upon more data points at different reaction conversions. However, to ensure that  $s$  is reported to an appropriate number of significant figures, the error associated with each measurement must also be considered.

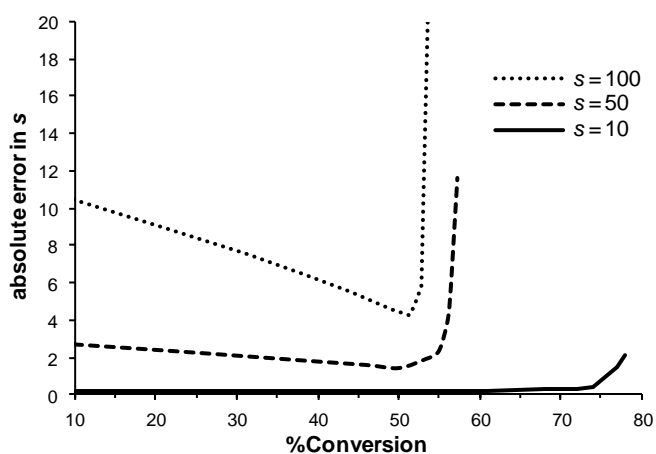


Figure 6. Absolute error in  $s$  as a function of reaction conversion.

### 2.5 Experimental reproducibility

As with all synthetic methods, it is important to assess the reproducibility of new KR methods to ensure any observed variations are within the expected analytical error range for a single experiment.

To quantify the reproducibility of a KR, in terms of both conversion and  $s$ , it is advisable to perform repeat experiments under analogous conditions. While it is practically unrealistic to perform repeat experiments for all substrates studied in a typical substrate class, it is recommended that (at a minimum) the reproducibility of a single representative example should be determined. Repeating a single experiment at least ten times will provide sufficient data to calculate reasonable mean and standard deviation values for calculated values of  $s$ . Taking the error as two standard deviations from the mean and comparing this value to the expected analytical error (as defined previously), provides a measure of the reproducibility of the KR. In cases where this ‘operational error’ significantly exceeds the expected analytical error, efforts should be made to rationalize the origin of the additional error(s) and adapt the experimental procedure accordingly.

### 2.6 Practical considerations for reporting $s$

Having assessed potential sources of error in  $s$ , it is worth considering their practical significance to outline some general guidelines for the best practice when reporting both analytically and practically meaningful values of  $s$ . From a practical perspective, the usual aim of a KR is recovery of substrate in highly enantioenriched form. The practical significance of  $s$  can therefore be assessed by the effect that differences in  $s$  have on the quantity of substrate that can be recovered at a specific level

of enantiopurity. For example, a selection of maximum possible yields of recovered substrate in 90, 95 and 99% ee for KR with  $s = 10\text{--}1000$  are given in Table 3. It is apparent that the practical difference in KR with  $s = 10$  and 20 is substantial (up to 10% yield difference for substrate recovery in 99% ee). The difference between  $s = 50$  and 100 is less significant (up to 2.5% yield difference for 99% ee); however there is still a meaningful practical distinction between these values. In addition, our analysis suggests  $s$  values of 100 carry an error of only around  $\pm 5$  (Table 2). Finally, for very high values of  $s$  ( $> 200$ ), the practical differences are very minimal. For example, the yield of recovered substrate in 99% ee in KR with  $s = 200$  and 1000 differs by just 1%. In practice, controlling reaction conversion to within 1% is challenging, and considering the large differences in rate constants for the reaction of each enantiomer of substrate, the reaction of the minor enantiomer is almost negligible in both cases.

Table 3. Maximum possible yields of recovered substrate of representative enantiopurities for KR with different  $s$

$s$	% Yield of recovered substrate with:			$\Delta\Delta G_{293\text{K}}^\ddagger$ <sup>a</sup>
	90% ee	95% ee	99% ee	
10	37.9	34.1	27.9	1.34
20	45.1	42.3	38.0	1.74
50	49.6	47.6	45.1	2.28
60	50.1	48.2	45.9	2.39
100	51.1	49.4	47.6	2.68
200	51.9	50.3	48.9	3.08
500	52.3	50.9	49.7	3.61
1000	52.5	51.1	50.0	4.02

<sup>a</sup> Energies given in kcal/mol

A final consideration for deciding the accuracy to which  $s$  should be reported is whether these values are useful to aid rationalization of KR selectivity. Computational methods are commonly used to model diastereomeric transition state structures (TSs) using the experimentally-determined differences in TSs energy ( $\Delta\Delta G^\ddagger$ ) to calibrate the method (Table 3).<sup>1,12,15</sup> For this purpose, the reporting of relatively high values of  $s$  (at least up to 200) could be beneficial.

Considering these practical points, in addition to the estimations of analytical error, the following guidelines should be considered when reporting  $s$ . For values of  $s$  below 50, we believe it is both analytically reasonable and practically informative to report these values to the nearest integer. For  $s$  above 50, as the analytical error becomes increasingly significant while the practical differences between  $s$  values diminish, it seems appropriate to report these values to the nearest 10. For very high  $s$  values, a suggested upper limit of  $s = 200$  is considered appropriate. A similar recommendation has been previously made for enzymatic KR.<sup>5</sup> Beyond this value the analytical error is considerable and the practical differences between KR are only minimal (see Tables 2 and 3). Where reporting a value of  $s$  beyond 200 is required, additional experiments, such as a linear regression analysis,<sup>13</sup> and an estimation of the associated error, should be undertaken to obtain a meaningful  $s$  value.

## 3. Conclusions

In this manuscript our opinions, based upon our own experience and referee comments, on best practice when using  $s$  as a metric to describe the efficiency of KR have been presented. One approach to estimate the analytical error associated with calculated values of  $s$  has been outlined. To summarize, the following recommendations should be considered for the appropriate use of  $s$ :

- i) Selectivity factor should be abbreviated as *s* (lowercase, italics) for consistency.
- ii) A suitable method must be used to determine ee values. Ideally, ee values for both product and recovered substrate will be obtained and used for the calculation of *s* (see equations 2–4). Calculated conversion values should be validated using a second method for at least one example where possible.
- iii) Good signal-to-noise ratio and baseline separation between peaks is required in the chosen analytical method to allow reliable quantification of ee.
- iv) The validity of using *s* as a metric to describe the efficiency of a KR should be determined by demonstrating that *s* is independent of reaction conversion. This can be achieved by performing a linear regression analysis.
- v) KR should be performed to ~50% conversion to minimize error in *s*.
- vi) The analytical error associated with measuring both ee and conversion should be considered, and the effect on the calculation of *s* evaluated (noting that errors are likely to vary with the absolute value of ee). For KR analyzed by HPLC our estimation of associated errors (e.g. equations 5 or 6) can serve as a guide.
- vii) Repeat experiments should be conducted to assess the experimental reproducibility of the developed method.
- viii) For KR with  $s < 50$ , *s* should be reported to the nearest integer.
- ix) For KR with  $s = 50\text{--}200$ , *s* should be reported to the nearest 10.
- x) The upper limit for reporting *s* should be 200, after which all values should be reported as  $s > 200$ .

We hope that practitioners working in the field of KR will consider the recommendations proposed herein when reporting KR data. Universal adoption of a consistent approach to reporting *s*, and appreciation of the associated errors, will address the ambiguity that is currently common within the literature.

#### 4. Experimental section

HPLC analyses were obtained on either a Shimadzu HPLC consisting of a DGU-20A5 degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven or a Shimadzu HPLC consisting of a DGU-20A5R degassing unit, LC-20AD liquid chromatography pump, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using either DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns. Chromatograms were processed and analyzed using the manual integration function within the Shimadzu LabSolutions software. Detailed procedures that outline our data analysis are provided in the supplementary material.

#### Acknowledgments

The research leading to these results has received funding from the ERC under the European Union's Seventh Framework Programme (FP7/2007–2013)/E.R.C. grant agreement 279850. J.E.T. thanks The Leverhulme Trust [Early Career Fellowship

ECF-2014-005] for financial support. A.D.S. thanks the Royal Society for a Wolfson Merit Award.

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### **Supplementary Material**

Supplementary material associated with this article can be found at: <https://doi.org/10.1016/j.tet.2018.XX.XXX>.