

On the Practical Limits of Determining Isolated Product Yields and Ratios of Stereoisomers: Reflections, Analysis, and Redemption¹

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Abstract: This paper examines the limits of accuracy in reporting isolated product yields (i.e., recovery of total mass from chromatography or extractions) as well as ratios of isomers determined by HPLC, GC, or NMR methods. Attention is directed to the magnitude of errors encountered in the HPLC or GC measurements of such ratios when these measurements are conducted without accurate calibrations or determinations of response factors for the particular isomers. Accurately defined mixtures of compounds (prepared by volumetric means) were examined by the above methods and the obtained measurements compared with the actual composition. The relative errors between *actual content* and the *measured values* are listed for all comparisons. In addition, accuracy in the determination of weight of a sample as a function of scale was also examined. The results are tabulated for comparison and suggestions are made to the reader as to how to avoid inaccurate reporting of experimental parameters. The authors hope that disclosure of these facts will result in new editorial policies requiring that a phrase '*dr or er ratios reported in this paper have not been validated by calibration*' be inserted into general experimental descriptions. In addition, such editorial policy should also discourage the use of terms '*de*' and '*ee*', as these descriptors do not provide accurate and meaningful information about stereoisomer composition. This latter issue has already been suggested in the literature on several occasions.

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Key words: accuracy of determination of ratios of stereoisomers, accuracy of weighing, accuracy of product yield determination, product content determination, errors in reporting of analytical data

1 Introduction

One who has been reading the literature concerned with organic synthesis in recent years, be it methodology, catalysis, or total synthesis of natural products, may have noticed considerable inflation in the values reported for isolated product yields, ratios of diastereomers, and enantiomeric excess values. A comparison of papers published during the period 1955 to 1980 with those published between 1980 and 2005 reveals that those from the more recent period frequently report isolated product yields of

reactions >95%. Such large values were rarely found in the older literature and are all but absent in *Organic Syntheses*, a journal that only publishes procedures that have been independently reproduced. The reporting of selectivity parameters, diastereomer or enantiomer ratios appears to follow a similar trend. Discussion of these trends is often a topic of casual conversations at conferences where professionals within the synthetic community readily reject the reality of isolated yields as high as 95%. Such reports at best may be attributed to the inability of the authors and research personnel to determine accurately the true content of the sample under scrutiny, at worst to deliberate manipulation of research data.

These issues have been discussed in the literature on several occasions, and attempts to analyze the causes for yield inflation have been made.² The causes for such inflated reporting of experimental parameters may include any of the following:

- (a) pressure on the community to produce evidence for new and highly selective methods;
- (b) perception by the referees or the editors that the value of a new reaction or its selectivity is directly proportional to the percent yield of product or high values of ratios of stereoisomers, respectively;
- (c) pressure on the community to produce better results at a faster pace;
- (d) lack of training of academic research personnel in accurate determination of sample content; and
- (e) the decrease in the scale of experiments (attributable mainly to the availability of high-field NMR) and consequently a decrease in the accuracy of mass measurements; or
- (f) deliberate adjustments in the reported values so as to increase the perceived impact.

It is hoped that occurrences of the last mentioned possibility are rare; however, the question of scientific misconduct and deliberate fraud has received increasingly more attention,³ especially in patent litigation where comparisons of published data with original research files are routinely made and discrepancies in reported yields and selectivity data have been noted.⁴

Which of these factors might be a major contributor to the improbable values that appear in the current literature is open to discussion; however, there is no doubt that the absolute reproducibility of modern synthetic methods is, because of inaccurate reporting of values, questionable, and

there exists a real possibility that the overall impact on and the utility of current literature to future generations will be minimized and that some of the results may be ignored altogether. There is also little doubt that experimental procedures in, for example, the *Journal of Organic Chemistry* (up to about 1985) are in fact easily reproducible (as are those published in *Organic Syntheses*) by anyone reasonably skilled in the art.

This paper examines the rational limits for recovery of the mass of product isolated by chromatography and for determinations of isomer ratios. We publish the results of these simple but carefully performed experiments in the hope that the members of the organic synthetic communi-

ty take notice and consider adjusting their reporting accordingly in future publications.

2 On the Question of Isolated Product Yields

Accurate determination of the true content of a sample is a non-trivial matter. The system of Good Manufacturing Practice (GMP), employed in the pharmaceutical industry, ensures meaningful and reliable results in terms of analyzing for content, including trace impurities. The procedures used by academic researchers often fall far short of accurate determination of product mass in a sam-

Biographical Sketches



Martina Wernerova was born in 1980 in Svidnik, Slovakia. After completing her B.Sc. (2001) and M.Sc. (2003) degrees at the University of Pavol Jozef Safarik in Kosice, Slovakia, she began her Ph.D. study at the Charles University in Prague, Czech Republic, and joined the Institute of Organic Chemistry and Bio-

chemistry of the Czech Academy of Science in 2005. Main interest during her research career focused on the stereoselective synthesis of capreomycin core, mechanism of epoxide and pseudoepoxide migration, synthesis of biologically active glycoconjugates, and chemical methodology. She has published five pa-

pers and one international patent. In 2009, before the formal completion of her Ph.D. degree, she joined the group of Professor Tomas Hudlicky at the Brock University in St. Catharines, Ontario, as a research fellow and investigated new methods for the synthesis of various opiate antagonists.



Tomas Hudlicky was born in 1949 in Prague, Czechoslovakia, where he received his elementary and middle school education. After several years of working as a process chemist apprentice and in other odd jobs in pharmaceutical chemistry, it became apparent that higher education opportunities were closed to him. In 1968, he emigrated to the U.S. with his parents and sister. Hudlicky's educational experience continued at Blacksburg High School, from which he dropped out in the spring of 1969. Accepted as a probational student at Virginia Tech the following autumn, he received his B.Sc. in chemistry in 1973, and went on to pursue graduate studies at Rice University under the direction of Professor Ernest Wenkert in the field of in-

dole alkaloid total synthesis, earning his Ph.D. in 1977. He then spent a year at the University of Geneva working under the late Professor Wolfgang Oppolzer on the synthesis of isocomene. In 1978, he joined the faculty at the Illinois Institute of Technology as an Assistant Professor and began the first phase of his research career in the field of general methods of synthesis for triquinane terpenes and other natural products containing five-membered rings by [4+1] cyclopentene, pyrroline, and dihydrofuran annulation methodologies. He returned to his alma mater, Virginia Tech, in 1982, and rose to the rank of Professor in 1988. One year later, at the 20-year class reunion of the Blacksburg High School class of 1969, he received his High School Diploma.

The next phase of his research involved the investigation of *cis*-cyclohexadiene diols in enantioselective synthesis. In 1995, he moved to the University of Florida in Gainesville. In 2003, Dr. Hudlicky accepted an offer from Brock University where he currently holds a position as Canada Research Chair. His current research interests include the development of enantioselective synthetic methods, bacterial dioxygenase mediated degradation of aromatics, design and synthesis of fluorinated inhalation anesthetic agents, synthesis of morphine and Amaryllidaceae alkaloids, and design of unnatural oligo-saccharide conjugates with new molecular properties. His hobbies are skiing, hockey, martial arts, and music.

ple — especially when the scale of experiments is very small (5–20 mg) and the errors in weighing⁵ of the isolated samples become significant. Although buoyancy factors can generally be neglected, the use of argon in the laboratory can lead to significant errors. For example, if the tare weight of a flask is determined in air, and then reweighed under argon, it should be remembered that the weight of the argon blanket is significant—approximately 1–2 mg/mL ($d = 1.784 \text{ g/L}$). In addition, the practice of evaluating yields by NMR, HPLC, or GC methods leads to inaccurate results because not all mass of the sample can be detected by these techniques or their combination. On preparatively useful scales, the dry weight of a sample that has passed combustion analysis coupled with the purity determination performed within the limits of detection by the above methods would suffice; however, the practice of including combustion analysis data in publications has all but vanished from current literature. In light of the apparent yield inflation in recent literature, we were curious about what rational limits of isolation exist for determination of isolated mass by procedures commonly used in academic laboratories, namely extraction, filtration, and column chromatography. We implemented techniques that are generally expected to be mastered by the time one reaches the stage of a mid-level graduate student. The average skill set available in academic laboratories was represented in these experiments by a late-stage Ph.D. student.

We chose several simple experiments in order to demonstrate recovery of mass from a sample subjected to several physical manipulations. We used *analytically pure compounds* (acetanilide and benzamide) on a scale of about one gram, accurately weighed before each experiment. The results are summarized in Table 1. Entry 1 provides percent mass recovery of acetanilide from simple filtration through a column of flash silica. The data in entry 2 provides the corresponding recovery data when multiple fractions were collected and later combined. Finally, entry 3 shows the results of careful chromatography of the two compounds with widely different R_F values (R_F acetanilide = 0.46, R_F benzamide = 0.31; EtOAc–hexane = 2:1).

The recovery of material clearly diminishes with each additional operation or handling and a full 2% of mass is lost on careful separation of the two pure components. Thus claims of 97–98% yields obtained by chromatography of crude products should be viewed with suspicion.

Table 1 Limits of Recovery of Mass from Chromatographic Separations

Entry	Weight average (mg)	Recovery average (mg)	Error/Yield (%)
1) Filtration ^a	1000.5	1001.7	0.1/ 100.1
2) Fraction collection ^a	1000.3	985.0	1.5/ 98.5
3) Separation ^a	1000.6	980.1	2.1/ 97.9

^aThe data reported represent an average of six individual experiments.

Table 2 Loss of Material in Extraction

Entry	Weight average (mg)	Recovery average (mg)	Error/Yield (%)
1) Extraction 4×2 mL ^a	1001.6	975.7	2.6/ 97.4
2) Extraction 1×10 mL ^a	1002.4	978.6	2.4/ 97.6

^aThe data reported represent an average of six individual experiments.

Table 2 shows the diminishment in recovery when the solution of acetanilide in EtOAc (1,000 mg in 100 mL) is first washed with brine, organic layer dried with MgSO_4 , filtered, and solvent evaporated. These experiments were chosen to demonstrate that each physical manipulation (including drying, filtration, and evaporation) of a sample is an opportunity for loss of material or an enrichment of a major component of an isomeric mixture in situations where such major component constitutes more than 90% of total mass. (For a more detailed discussion of enrichment factors resulting from physical manipulation of mixtures see reference 1b, Part 2, pages 93–95.)

The results presented above point to very clear conclusions with regard to what can be considered as reasonable recovery of a compound from chromatographic separations that are also preceded by standard work-up procedures. In all manipulations of these pure compounds a *minimum of about 1–2% per manipulation was lost* from the total. In one case the amount recovered was actually larger, possibly because of particulate matter (i.e., silica) washed into the solution (such additional ‘weight’ might also contribute to the inflated reaction yield values, especially at smaller scales) or simple errors in weighing. The experiments were performed with analytically pure samples, which, of course, do not contain the polar materials that usually show up at the origin upon TLC analysis of crude reaction products.

Given that most academic groups do not subject day-to-day reactions to serious optimization or matrix-optimization⁶ as is done in industry, it is reasonable to assume that the vast majority of the reactions reported in the literature do not proceed with quantitative conversions. Such aspect would approximate our experiments with mixtures of pure compounds. Because a minimum of three operations (extraction, filtration, and evaporation) is required in working up most reactions, we conclude that *yields higher than ca. 94% obtained by work-up and chromatography of crude reaction mixtures are likely unrealistic and erroneous in nature*. Such values may arise as a direct consequence of not following correct protocols, which would be expected in the fast-paced academic environment. (An astute student of the organic literature may discover that this very author has been guilty of reporting yields in this range from time to time!)

A further complication exists in reporting realistic yields, especially overall yields, of a longer sequence, such as that of any total synthesis. Unless the sequence is performed on a scale large enough to permit isolation of rea-

sonable amounts of analytically pure materials (i.e., milligram or higher), the errors in weighing small amounts of material are compounded and lead to misleading values. (See the next section for an evaluation of such errors.) Most academic syntheses yield milligram amounts of the final product. The accuracy in calculating the overall yields of such sequences is clearly questionable, and the information content in the value of an overall yield therefore has little meaning. There are much better methods available for the evaluation of efficiency of a particular process. Metrics that have been developed to account for product/waste ratios offer more accurate details of reaction or process efficiency than percent or overall yields.⁷ The evaluation of synthetic sequences by such metrics is far more meaningful than the provision of overall yields. A review by Andraos⁸ provides a guide to these methods, which were used recently to compare the overall effectiveness of the many academic and industrial syntheses of oseltamivir (Tamiflu).⁹

3 On Determination of Accurate Weights

The accuracy of reported product yields depends on an accurate determination of sample content and accurate determination of mass. The former should be attended to by the choice and combination of appropriate analytical methods, whereas the latter is a function of scale. In a typical total synthesis the amount of material diminishes as the length of the sequence increases. As a consequence, as

Table 3 Error in Weighing as a Function of Scale^a

Actual weight (mg)	Observed weight (mg)	Maximum observed error (%)
100	99.4–101.5	1.5
50	48.8–50.8	2.4
20	19.5–20.4	2.5
10	9.7–10.5	5.0
5	4.9–5.4	8.0
3	2.4–3.2	20.0

^a The data reported represent an average of six individual experiments.

Table 4 Error in Weighing as a Function of Sample Amount and Container Volume^a

Flask volume (mL)	Difference in weight of empty flask ^{b,c} (mg)	5 mg Error (%)	20 mg Error (%)	100 mg Error (%)
250	7.0	140	35	7
100	3.9	78	20	4
50	2.1	42	11	2
25	1.6	32	8	2

^a Weights are averages of four weighings.

^b Weight of dry flask from desiccator.

^c Weight of flask and sample open to air.

the synthesis progresses, the measurements are obtained on smaller and smaller amounts and the errors made during weighing at each step are compounded to a point where the value for the overall yield is meaningless.

Table 3 shows the relative errors as a function of the quantity being weighed. In each case, the actual amounts were accurately provided by evaporation of an appropriate volume of a standard solution (benzamide) prepared by volumetric means. It is clear that the error increases with the decreasing scale and becomes greater than 10% below 4–5 mg. Any yield calculation at scales below 5 mg therefore cannot accurately reflect reality.

To make matters more complicated, the size of the container in which the weight determination is made may contribute to additional inaccuracy of the overall measurement. Table 4 shows the errors in determination of different amounts of sample in containers of varying volume that were either open to ambient atmosphere or dried in the oven and kept in a desiccator prior to weighing.

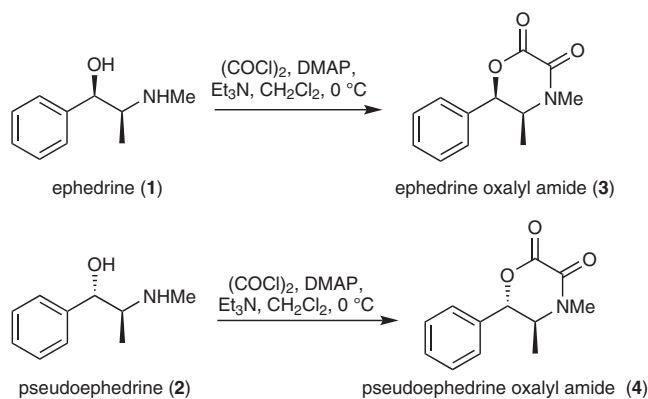
In weighing empty flasks ranging in size from 10 to 250 mL there is a consistent trend in decreasing accuracy as a function of volume (approximately 0.6 mg for each 10 g of container weight). A similar trend was observed when weighing accurately determined amounts of sample in the same series of containers. These experiments indicated that the smaller the weight of actual sample and the larger the container, the larger the percent error in the determination of sample weight, as shown in Table 4. Thus, it is evident that the values of reported yields depend greatly on the scale of experiment as well as on the method by which the sample weight and content are determined.

4 On the Question of Accurate Detection of Stereoisomer Ratios

With respect to limits of detection of isomer ratios we were curious as to the difference in determination of ratios by the usual methods (i.e., GC, HPLC, NMR) without and with proper calibration. In the academic setting it is not a common practice to determine response factors or construct careful calibration curves. The ratios obtained by analyzing mixtures of diastereomers or enantiomers are usually reported as obtained by the measurement. On the other hand, precisely defined protocols exist for quantitative determination of content, but these are almost never

followed in academia (as ascertained by many conversations with colleagues and their students, who readily admit that the results reported represent raw data obtained by integration and that no calibrations were performed because of the effort that would be required to do so). It is apparent from our experiments that most of the data reported in the literature is in fact misleading and grossly inaccurate because proper protocols were not followed.

For the analysis of diastereomer ratios we chose mixtures of two similar compounds. Ephedrine (**1**) and pseudoephedrine (**2**) were converted into their oxalyl amide derivatives **3** and **4** (Scheme 1), respectively, as these compounds are more stable to manipulation and provided better separation on GC and HPLC. For the determination of enantiomer ratios, a variety of mixtures of (+)-(*R*)-phenylethanol and (–)-(*S*)-phenylethanol were chosen. The mixtures of diastereomers were analyzed by gas chromatography, HPLC, and ¹H NMR, while those of enantiomers were subjected to HPLC analysis on a chiral support. In each case a standard solution was prepared by means of accurate volumetric methods and subjected to careful analysis.



Scheme 1

Because of the close similarity of the two compounds the response factor of detection (flame ionization in GC and UV detection in HPLC, respectively) was initially not taken into account. The results are shown in Tables 5–7. These results clearly show that reported ratios of isomeric mixtures that are greater than 200:1 should be viewed as inaccurate unless other methods of detection are used, such as co-injection of known amounts of standards followed by calibration. Furthermore, diastereomer or enantiomer ratios of products corresponding to 200:1 or more would imply energy differences of more than 3 kcal/mole for reactions leading to such mixtures; such a difference seems unlikely for closely related compounds.¹⁰ If indeed stereoselectivity greater than 200:1 is attained in a reaction (certainly possible in enzyme catalysis), the manipulation of such a mixture by physical means would lead to a complete loss of the minor component because of continuous enrichment of the major one, as pointed out above.

Table 5 shows the results of analysis of standard solutions prepared by volumetric methods by GC, HPLC, and ¹H NMR. The results are reported *as obtained by integration*. Approximate calibration (not GMP protocol) was made only for the HPLC experiments, and it is clear that the results from calibration experiments are closer to actual values. In Table 6 the results of analysis are reported for mixtures with ‘inverted ratios’. These results show that the accurate determination of the ratios at high dilutions is difficult, even with calibration, because of the non-linear response of the component at low concentration (Beer’s law). The response factors for **3** and **4** and the calibrations were determined as follows.

Calibration curves for both isomers were determined for concentrations of 1, 10, 100, and 1000 ppm. Isomer **4** displayed a slightly lower response than **3**, with a correction of 1.054 at a concentration of 100 ppm, the same concentration as our mixture of isomers. Because the response factor at the lowest concentrations was non-linear, a correction factor of 1.054 was applied to the value of prevailing isomer. The values for **4** were multiplied by 1.054 in Table 5 to arrive at the calibrated ratios; conversely, the values for **3** in Table 6 were divided by 1.054.

Table 5 Comparison of the Actual Ratio of Two Diastereomers with the Ratios Determined by HPLC, GC, and ¹H NMR

Actual ratio 4/3	Ratio by NMR	Ratio by GC	Ratio by HPLC	Ratio by HPLC with calibration
50:50	51:50	50:50	48:50	51:50
75:25	75:25	73:25	71:25	74:25
80:20	87:20	82:20	74:20	78:20
90:10	91:10	97:10	85:10	89:10
95:5	98:5	100:5	95:5	100:5
99:1	110:1	63:1	87:1	92:1
199:1	226:1	83:1	152:1	161:1

Table 6 Comparison of the Actual Ratio of Two Diastereomers with the Ratios Determined by HPLC and GC. Real Ratio is Opposite to the One in Table 5

Actual ratio 4/3	Ratio by HPLC	Ratio by HPLC with calibration	Ratio by GC
50:50	50:52	50:49	50:50
25:75	25:80	25:76	25:78
20:80	20:84	20:80	20:83
10:90	10:85	10:81	10:89
5:95	5:105	5:99	5:121
1:99	1:111	1:106	1:118
1:199	1:214	1:203	1:142

The data in Tables 5 and 6 demonstrate that HPLC and NMR are superior to GC analysis (uncalibrated) for ratios of diastereomers up to 95:5. Various methods of determination of diastereomer ratios (*dr*) by NMR as well as enantiomer ratios (*er*) via Mosher esters have been published, including methods based on ^{11}B NMR.¹¹ The publications generally claim accuracy of 1–3% as determined by careful integration.¹² In this regard it is interesting to note that the old method of cutting and weighing of NMR peak areas is just as accurate as or even more accurate than integration. For example, (+)- and (–)-ephedrine hydrochlorides were analyzed as their diastereomer complexes with chiral salts by ^1H and ^{13}C NMR, and the results of integration compared with cutting and weighing showed detection limits of 1% with precision of $\pm 0.5\%$.¹³ Claims of accuracy of NMR methods beyond the ratios of 98:2 are rare. A recent paper claimed accuracy of 1000:1 (99.8% de) in the determination of ratios of ephedrine derivatives;¹⁴ however, a close examination of the methods described in this report revealed that the usual hardware limitations of NMR instruments were probably not taken into account. The dynamic range (the detection of the strongest versus the weakest signal before saturation) and the relatively low molecular weight of the ephedrine derivatives bring to question the validity of measurements beyond the usually accepted accuracy range of 1–2%.

The analysis of ratios of the two enantiomers of phenylethanol on a chiral support is shown in Table 7. The analysis is reasonably close to the actual values, but provides poor correspondence beyond a ratio of 100:1. Because ratios of enantiomers can also be determined by derivatization techniques, the experiment with Mosher's acid chloride was performed for comparison. The mixture of 1-phenylethanol (*S/R* = 95:5) in CDCl_3 was first measured by HPLC on a chiral support. After the transformation of the mixture to the corresponding Mosher's esters,¹⁵ the diastereomer ratio was determined by NMR methods. Table 8 compares the results of observed ratios by HPLC, ^1H NMR, and ^{19}F NMR.

It is important to point out that in the experiments with mixtures of stereoisomers there will be a built-in error as the initial determination of purity of commercially avail-

Table 7 Comparison of the Actual Ratio of Two Enantiomers with the Ratio Determined by HPLC Analysis on Chiral Support

Actual ratio <i>R/S</i>	Ratio by HPLC
50:50	50:52
25:75	25:75
20:80	20:80
10:90	10:92
5:95	5:99
1:99	1:109
1:199	1:272

Table 8 Comparison of the Actual Ratio of Two Enantiomers with the Ratio Determined by HPLC Analysis on Chiral Support, ^1H NMR, and ^{19}F NMR

Actual ratio <i>S/R</i>	Ratio by HPLC	Ratio by ^1H NMR	Ratio by ^{19}F NMR
95:5	105:5	109:5	103:5

able materials is performed by HPLC, a method proven not to be exceedingly accurate for mixtures beyond a ratio of 95:5. In addition, because the rates of reactions of the two enantiomers with a chiral reagent or the corresponding free energy of adsorption on a chiral support are different, the enrichment of one or the other component may lead to inaccurate determination of true ratios unless careful calibration is performed. In separations of non-racemic mixtures of enantiomers on an achiral support great care must be taken to avoid any local enantiomeric enrichment of certain purified fractions whose analysis would then provide false information about the initial composition of the reaction mixture, as pointed out by Dreiding.¹⁶ These and other aspects of correct analytical protocols must be taken into account to ensure meaningful accurate results.

5 Conclusions

The conclusion drawn from this set of experiments points to the prevalence of serious discrepancies in the reporting of values for yields and ratios in the current literature. We have demonstrated that the facilities and equipment available in a typical academic laboratory are not adequate to support the accuracy of claims frequently made in the literature. Furthermore, given the average skill set of academic personnel, it seems unrealistic to expect that the majority of reported reactions have been subjected to serious optimization beyond 95% product content (not to be confused with isolated product yield) and that careful and analytically accurate methods for the determination of mass content of product were followed. We hope that the synthetic community will seriously consider reporting of ratios of diastereomers or enantiomers accompanied by a short statement reflecting the authors' performance of calibrations or the absence thereof (as is frequently done with the reported values of melting points). Without such a disclaimer the values have little or no meaning, as we have, hopefully, demonstrated in this paper. In addition, the reporting of yields would best be done by stating the *range* of isolated yields along with evaluating the *conversion* of the starting material and the detection method used to evaluate it.

Thus, we suggest the following to implement the much-needed improvements in the integrity of current literature:

The experimental section should contain either evidence of calibration or a disclaimer thereof when reporting *dr* or *er* as measures of stereoselectivity.

The usage of *de* and *ee* should be discontinued immediately. Gawley's report¹⁷ clearly indicates that *dr* and *er* are better and more accurate evaluations of stereoselectivity.

Isolated yields of products should be reported by indicating a range of yields obtained whenever multiple experiments were performed. Percent conversion of the starting material into product should be provided along with the method of determination.

The usage of terms such as 'efficient' or 'practical' applied to methodology or total syntheses should be discouraged, or even eliminated, from publications unless supported by actual efficiency evaluation by some of the available metrics.

The editorial policies of journals reporting on organic synthesis should be amended to require the above recommendations.

We hope that the synthetic community's reflection on the results presented here may lead to new editorial policies in those journals that publish research on stereoselective organic synthesis. The current practice of reporting unrealistically high isolated product yields and stereoisomer ratios creates serious problems in reproducibility and hence leads to diminished credibility of the authors. These aspects require serious attention and focus to ensure proper training of future generations of students.

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